Data-Driven Approaches to Frailty Operationalization and Prediction of Adverse Outcomes

by

Linzy Michelle Bohn

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Psychology

University of Alberta

Abstract

Objective: We advance the literature on frailty measurement and conceptualization by applying data-driven analytic technologies to multiple aging morbidity indicators in order to detect clusters of deficits or individual features that elevate risk for (a) frailty emergence and progression and (b) adverse cognitive outcomes or trajectories. Studies 1-3 are presented in Chapters 2-4, respectively. In Study 1, we examined whether baseline frailty profiles could be empirically determined; extracted profiles predicted frailty progression and neurocognitive slowing; and results generalized across sex. In Study 2, we aimed to extract longitudinal frailty profiles (or statuses); characterize patterns of frailty progression; and identify predictors of baseline frailty classifications and transitions. In Study 3, we sought to identify frailty-related features that increase risk for cognitive impairment and dementia; calculate a data-driven frailty index; and (c) examine whether frailty levels vary across clinical cohorts and complementary frailty index operationalizations.

Overall Method:

Study 1 participants (n = 649) were cognitively normal (CN) adults from the Victoria Longitudinal Study who contributed data for baseline multi-morbidity assessment and longitudinal trajectory analyses. Exploratory factor analysis (EFA) was applied to 50 multi-morbidity items, revealing 7 separable domains. The proportion of deficits accumulated in each domain was submitted to latent profile analysis. The extracted profiles were tested as predictors of level and change trajectories in a 50-item frailty index and a latent neurocognitive speed variable.

Study 2 participants (n = 3,074) were clinical cohorts from the National Alzheimer's Coordinating Center with amnestic mild cognitive impairment (aMCI) or Alzheimer's disease

(AD). Participants contributed baseline and 2-year follow-up data for 43 multi-morbidity items and baseline risk characteristics for prediction analyses. EFA was applied to 43 multi-morbidity items, revealing 5 separable domains. The proportion of deficits accumulated was submitted to latent transition analysis.

Study 3 participants (n = 255) were from the Comprehensive Assessment of Neurodegeneration in Aging. Participants contributed cross-sectional aging morbidity indicators (n = 84). We used random forest analysis to identify the most important features that discriminate cohorts with subjective cognitive impairment (SCI), MCI, or AD from CN controls. A 30-item data-driven frailty index and a complementary 81-item index was calculated.

Results:

Study 1: We detected three early frailty profiles: *not-clinically frail* (84%), *mobility-type frailty* (9%), and *respiratory-type frailty* (7%). Mobility-type frailty predicted accelerated deficit accumulation and neurocognitive slowing, followed by respiratory-type frailty, and not-clinically frail. Results were robust across sex.

Study 2: We detected two baseline statuses: *Not-Clinically Frail* (91%) and *Moderately Frail* (moderate ambulatory impairment endorsed; 9%). At follow-up, *Not-Clinically Frail* (56%), *Moderately Frail* (19%), *Mildly Frail* (mild ambulatory impairment; 21%), and *Severely Frail* statuses (severe ambulatory impairment; 4%) were detected. Moderately Frail participants were more likely to remain in statuses characterized by a higher frailty burden, and discriminated by age, male sex, AD diagnosis, and global cognition.

Study 3: Central risk elevating characteristics included quality of life (QoL), lymphocytes, and neutrophils for SCI; QoL, male sex, lymphocytes, and eyesight for MCI; and QoL, olfaction, visual contrast sensitivity, male sex, and instrumental activities of daily living for AD. We also

detected features that were selectively sensitive to SCI, MCI, and AD. Clinical cohorts reported (a) comparable levels of frailty and (b) higher levels of frailty on the 30-item index as compared to CN controls and the 81-item index.

Discussion: In a programmatic series of three studies, this dissertation research applied a suite of data-driven technologies to the challenge of resolving several empirical and clinical inconsistencies in the multi-morbidity and aging literature. Study 1 provides novel insight into critical early domains of frailty (e.g., mobility impairment) that serve as portals into broader and chronic frailty. Study 2 demonstrated that these domains are relevant for aMCI and AD in that (a) frailty statuses varied along a continuum of ambulatory impairment and (b) moderate impairment exacerbated risk for adverse frailty transitions. Study 3 identified selected important features of frailty that elevate clinical risk for SCI, MCI, and/or AD. Overall, these results demonstrate that some features of frailty are important across a clinical spectrum of aging and AD and thus may increase prediction accuracy in clinical-research setting. Further, early interventions targeting mobility and related functional impairments may prevent frailty emergence and progression, as well as downstream negative outcomes.

Preface

Chapter 2 and Appendix A of this dissertation have been published as L. Bohn, Y. Zheng, G. P. McFall, and R. A. Dixon, "Portals to Frailty? Data-Driven Analyses Detect Early Frailty Profiles," *Alzheimer's Research & Therapy*, 2021, vol. 13, issue 1, 1-12. https://doi.org/10.1186/s13195-020-00736-w. LB, GPM, and RAD were responsible for the conception and background. LB, YZ, GPM, and RAD were responsible for the design and analysis plan. LB, YZ, and GPM were responsible for data assembly and statistical analyses. LB, YZ, GPM, and RAD were responsible for interpretation of the results. LB drafted the manuscript. YZ, GPM, and RAD critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. We present the final accepted version of the pre-publication manuscript and supplementary material.

Dedication

To my beloved husband, Darren, for his unwavering support, sacrifice, and encouragement—thank you.

To my daughters, Lola and Ivy, whom I deeply adore. You can achieve anything through faith and patient endurance.

To my parents, Dale and Brenda, for inspiring this journey, setting me off with a belief that I could succeed, and modelling the skillset required to do so.

To my mother-in-law, Sherril, for supporting me in matters both big and small.

This work is the culmination of our efforts.

Acknowledgements

I would like to express my sincere gratitude to my supervisor, Dr. Roger Dixon, whose direction, insight, patience, and understanding enabled me to see this project through to completion. I am deeply appreciative of your support. To my committee members, Drs. Tammy Hopper and Christina Gagne, for graciously lending their time and expertise. To my mentors, both past and present, including Drs. Peggy McFall, Sheree Kwong See, Al Dobbs, and Sandy Jung, for inspiring, encouraging, and facilitating my academic pursuits. To my friends, for offering a sympathetic ear and welcomed distraction.

Funding Acknowledgement: The research in the three studies reported in this dissertation were supported by grants to Roger A. Dixon. We acknowledge: (a) Partnership support from the Canadian Consortium on Neurodegeneration in Aging and research funding from Alberta Innovates and the Canadian Institutes of Health Research (CAN-163902), (b) National Institutes of Health (National Institute on Aging; R01 AG088235), and (c) the Canada Research Chairs program. Linzy Bohn was supported by a doctoral fellowship from the Social Sciences and Humanities Research Council of Canada.

The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI

Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

Table of Contents

List of Tables

List of Figures

Chapter 1: General Introduction

Global life expectancy at birth has risen dramatically over the course of history. Early gains were attributed to organized efforts to control the spread of infectious disease, as well as declines in infant and child mortality rates (Wilmoth, 2000). Since the 1970s, the primary factor contributing to rising life expectancies in developed high-income countries (Kontis et al., 2017) are reduced mortality rates amongst older adults, particularly those that are attributed to non-communicable diseases (e.g., cardiovascular disease or cancer; Mathers et al., 2015). The rate of these improvements varies by geographic location. A recent study ranked 53 high-income countries by the average annual rate of increase in life expectancy for males and females at the age of 60 over the period of 1980-2011 (Mathers et al., 2015). The greatest annual gains were recorded for males in New Zealand (0.22) and females (0.24) in Japan. Put into context, these values indicate that life expectancy for 60-year-old Japanese females has been increasing at an average rate of 6 hours per day, or nearly a quarter of a year per year. Canada and the United States (US) ranked respectively as 13th (0.9) and 24th (0.8) for males, 26th (0.5) and 38th (0.4) for females. Current estimates of maximum life expectancy at birth is 78.3 years for Canadian males and 83.0 years for Canadian females (Barthold et al., 2014). Maximum life expectancy at birth for American males and females is comparatively lower at 75.3 years and 80.4 years, respectively (Barthold et al., 2014). These trends, together with the aging of the baby boom generation (the oldest of which turned 74 in 2020), has led to a rising number and proportion of North Americans aged 65+ (Alzheimer's Association, 2016). The most recent prevalence estimates in this age bracket are 16.2% in the US and 17.6% in Canada (World Bank, 2019).

Because chronological age per se is the single most predictive biomarker of Alzheimer's disease (AD; the most common cause of dementia), the prevalence of AD is expected to increase

dramatically in the coming years. In 2016, an estimated 564,000 Canadians had a diagnosis of dementia. By 2031, this number is expected to increase to 937,000 (Alzheimer Society of Canada, 2016). The incidence of AD is projected to increase from 1 new case every 5 minutes to 1 new case every 2 minutes over this same time frame. The individual and societal impact of AD is considerable (Alzheimer Society of Canada, 2016; Alzheimer's Association, 2016; Public Health Agency of Canada, 2019). Males with AD or a related dementia lose an average of 16.0 years of life in full health due to disability and premature death, while females lose an average of 15.2 years in full health due to these same considerations (Bray & Huggett, 2016). Direct healthcare costs, unpaid caregiver opportunities, and indirect costs associated with the provision of unpaid care are expected to cost Canadian society upwards of $872 billion over the next 30 years (Alzheimer Society, 2010). Notably, there are currently no medications approved for AD prevention or treatment, despite the emergence of powerful large-scale observational studies and carefully designed clinical trials (Cummings et al., 2019). Consistent failures of pharmaceutical interventions are attributed to lack of efficacy, excessive side effects, and/or difficulties in clinical trial execution (e.g., protracted time frame required to recruit study participants or determine whether the investigational treatment alters disease progression; Alzheimer's Association, 2019; Cummings et al., 2014). The success rate for AD drug development may improve as knowledge on the complex neurobiology of AD advances and/or novel disease pathways that are amenable to pharmacological intervention are identified.

Identification of modifiable risk factors that may inform secondary prevention strategies is another critical area of research attention (Anstey et al., 2015; Dixon & Lachman, 2019; Livingston et al., 2017). In fact, dementia prevention was recently established as a leading objective in Canada's first national dementia strategy (Public Health Agency of Canada, 2019).

This objective encompasses (a) evidence-based identification and assessment of modifiable risk and protection factors, (b) risk reduction and protection elevation in older adults who are demonstrating normal brain and cognitive aging, and (c) design and implementation of interventions directed towards slowing progression of cognitive decline or impairment in older adults with minor neurocognitive disorders. Non-modifiable risk factors include important risk elevating characteristics such as chronological age, sex, and AD genetic risk loci, whereas modifiable risk factors include potentially reversible or controllable characteristics, such as hearing loss, social isolation, and hypertension (Livingston et al., 2017; Public Health Agency of Canada, 2019). A recent systematic umbrella review reported that low education, diabetes, smoking, depression, high homocysteine, and midlife obesity are modifiable risk factors that reliably predicted an increased risk for AD (Anstey et al., 2019). Physical activity, fish consumption, light alcohol consumption, and statin use are modifiable risk factors that reliably predicted a reduced risk for AD. The authors cautioned, however, that there remain considerable gaps in the literature on dementia risk factors. For example, few studies have sought to develop more nuanced approaches to dementia risk reduction (e.g., personalized interventions tailored to specific subgroups of older adults). This is a priority area, as even a modest reduction in modifiable risk factor prevalence may delay or prevent a third of dementia cases (Livingston et al., 2017).

Accumulating longitudinal research highlights that non-modifiable and modifiable risk factors may independently or interactively contribute to substantial variability in level and change trajectories across multiple domains of brain and cognitive functioning. These domains include indicators of structural and functional neuroimaging (Harada et al., 2013; Nyberg et al., 2012; Raz et al., 2010), episodic and semantic memory (Josefsson et al., 2012; McFall et al.,

2019; Nyberg et al., 2012), executive functions (de Frias et al., 2009; Lin et al., 2017), neurocognitive speed (Bott et al., 2017; Lin et al., 2013), and global cognition (Hayden et al., 2011; Hochstetler et al., 2016; Yaffe et al., 2009). This dynamic heterogeneity has been linked to a range of cognitive change trajectories and clinical outcomes, including cognitively stable or elite (Borelli et al., 2018; Dixon & de Frias, 2014), cognitively normal (CN; Harada et al., 2013), mild cognitive impairment (MCI; Kim et al., 2019), and dementia (Zahodne et al., 2016). Several recent reviews (Anstey et al., 2015, 2019; Dixon & Lachman, 2019) highlight that these cognitive phenotypes are jointly produced by modalities of non-modifiable and modifiable risk factors, including genotype (e.g., Apolipoprotein E), environment (e.g., air pollution, pesticides, and lead exposure), and behavioral and lifestyle factors (e.g., sleep, attitudes towards aging, and cognitive activity).

Notably, frailty may also account for variability in cognitive aging trajectories (Brigola et al., 2015; Canevelli et al., 2015; Robertson et al., 2013). Frailty reflects a state of increased vulnerability to relatively minor stressors due to age-related declines in multiple interrelated physiological and health systems, leading to reduced homeostatic reserve and resiliency (Clegg et al., 2013). A systematic review based on 21 cohorts involving 61,500 community dwelling participants reported that, on average, 10.7% of adults aged 65 and up are frail and 41.6% are pre-frail (Collard et al., 2012). Further, the prevalence of frailty was reported to increase with age, and more females than males are frail. The prevalence of frailty is even higher in continuing care settings. A recent meta-analysis reported that 52% of older adults in long-term care facilities are frail and an additional 40% are pre-frail (Kojima, 2015). These estimates are concerning, given that frailty has been characterized as one of the most problematic expressions of population aging (Clegg et al., 2013). Higher levels of frailty predict an increased susceptibility

to numerous additional adverse outcomes, including falls, incident disability, institutionalization, hospitalization, and mortality (Clegg et al., 2013; Gonzalez-Colaço Harmand et al., 2017; Rockwood et al., 2007). Understanding frailty and its impact is thus a pressing clinical and research priority (Lim et al., 2018).

Currently, two approaches to frailty measurement and conceptualization predominate: the physical frailty phenotype and the frailty index. The former approach was developed and validated by Fried and colleagues using data from the Cardiovascular Health Study (Fried et al., 2001) and operationalizes frailty as a characteristic syndrome that is marked by the presence of three of the following five features: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. Older adults with none of these features are considered robust, while those with one or two of these features are considered pre-frail. The latter approach was developed and validated by Rockwood and colleagues using data from the Canadian Study of Health and Aging (Mitnitski et al., 2001) and operationalizes frailty as a state of age-related deficit accumulation that can be quantified in a frailty index. A continuous frailty index is formed by calculating the ratio of deficits present in a given individual relative to the total number of deficits considered.

Considerable debate abounds in the literature as to which of these operationalizations is most suitable for clinical and/or research application (Rockwood & Howlett, 2018). A strength of the frailty phenotype is that it can be applied at first contact with an older adult and does not require a preliminary clinical evaluation (Cesari et al., 2014). This approach thus easily lends itself to the initial stratification of older adults into discrete categories of frailty risk (i.e., robust, pre-frail, and frail). However, it has been expressed that, because the frailty phenotype considers only a pre-determined and restricted number of physical and performance-based characteristics,

it may (a) not afford understanding of what preventative or therapeutic interventions are required, (b) lack sensitivity to early stages of risk, and (c) show ceiling effects (Cesari et al., 2014; Lacas & Rockwood, 2012). Indeed, several studies show that, relative to the frailty index which permits a finer gradation of risk, the phenotype has both limited discriminatory ability for older adults with moderate or severe frailty and less predictive value for negative outcomes (Kulminski et al., 2008; Rockwood et al., 2007). Conversely, a frailty index can be calculated using a wide array of clinical symptoms, signs, diseases, disabilities, and abnormal laboratory values providing that the following criteria are satisfied: biologically sensible, accumulates with age, does not saturate too early, and covers a range of aging systems (Searle et al., 2008). This approach may not be feasible at first contact with an older adult, however, once the frailty index has been calculated, it has considerable utility for examining trajectories of multi-morbidity over time and determining the effectiveness of an intervention (Cesari et al., 2014). Moreover, because there are few restrictions on what deficits can be included in a frailty index, this approach is useful for secondary analysis of existing longitudinal data sets that did not initially purport to investigate frailty (Lacas & Rockwood, 2012; Thibeau et al., 2019). Nevertheless, this approach is not without criticism (Walston et al., 2006). Chief amongst these is that the number of equally weighted deficits is taken as the measure of accumulated vulnerability and susceptibility to adverse outcomes. This raises the possibility that distinct (and even unexpected) clusters of aging morbidity may serve as (a) domain-specific intensifiers of frailty effects on adverse aging outcomes or (b) early signals or even portals to emerging global and chronic frailty. Neither current approach to frailty assessment is optimally suited to investigate these possibilities.

Notably, growing research attention has been directed towards identifying novel approaches to frailty measurement and conceptualization that may produce some resolution of contradictions or inconsistencies between prevailing frailty models (Anstey & Dixon, 2014; Clegg et al., 2013; Fulop et al., 2010; Rockwood & Howlett, 2018; Walston et al., 2018). Accordingly, this program of dissertation research aimed to (a) develop an unbiased approach to measuring and conceptualizing frailty and (b) detect data-driven frailty clusters or profiles that portend an increased risk for negative cognitive aging trajectories and/or clinical outcomes. Research investigating these aims has implications for both concurrent identification of frailty and early detection of elevated frailty risk. We examined these research aims using contemporary and data-driven (as opposed to hypothesis-guided) analytical approaches. Specifically, we employed structural equation modeling (e.g., latent growth curve models), mixture modeling (e.g., latent profile analysis [LPA] and latent transition analysis [LTA]), and machine learning technologies (e.g., random forest [RF] analysis). Data-driven approaches provide a potentially powerful technology for studying heterogeneous clinical syndromes for which there is limited consensus on its defining and emergent characteristics. A potential outcome of these approaches is unbiased discovery of distinct frailty profiles that may overlap with some phenotypes but may also reflect novel combinations of indicators of aging multi-morbidity. These profiles may represent subgroups of older adults who are at increased risk for frailty emerge and progression, as well as adverse frailty-related outcomes.

This dissertation presents a programmatic series of three studies that integrated the main research components outlined above. Specifically, we applied data-driven analytical techniques to the analysis of large-scale, multi-domain data sets in order to develop an empirically refined operational conceptualization of frailty. Large-scale longitudinal studies of human aging provide

an ideal platform for these investigations because they (a) implement comprehensive measurement batteries that span multiple domains of aging morbidity (e.g., biological, functional, health, genetic, neuropsychological, and lifestyle characteristics), (b) involve varied samples and clinical cohorts (e.g., normal cognitive aging, impairment, and dementia) that span broad bands of aging (e.g., mid- to later-life), and (c) lend themselves to understanding profiles, patterns, predictors, and outcomes of frailty.

The present studies begin with data-driven analyses conducted on the following three large-scale data sets: Victoria Longitudinal Study (VLS), National Alzheimer's Coordinating Center (NACC), and The Comprehensive Assessment of Neurodegeneration and Dementia Study (COMPASS-ND). In Study 1, we applied LPA to baseline multi-morbidity indicators from the VLS in order to detect underlying early frailty profiles in CN older adults. In Study 2, we applied LTA (a longitudinal extension of LPA) to two waves of multi-morbidity data from the NACC in order to detect frailty profiles in clinical cohorts of older adults who are classified at baseline as having amnestic MCI (aMCI) or AD. In Study 3, we assembled cross-sectional multi-morbidity data from the COMPASS-ND database and employed RF analysis in order to identify the most important frailty-related features that discriminate clinical cohorts of older adults with subjective cognitive impairment (SCI), MCI, or AD from a benchmark sample of CN controls. In each of the respective studies, we evaluated the predictive validity of our data-driven frailty models concurrently by examining the extent to which they predict frailty emergence and progression and/or negative outcomes across a spectrum of normal cognitive aging through to impairment and dementia.

Organization of the Dissertation

We turn now to a brief overview of the three studies that comprise the dissertation research. We present separate, detailed descriptions of each study in Chapters 2–4. Specifically, in each of the latter chapters we outline the relevant literature, methods, results, and conclusions. Tables and figures for each study are presented at the end of the corresponding chapter. References for each chapter are presented at the end of the dissertation. Supplementary material for Chapter 2 is presented in Appendix A (at the end of the corresponding chapter). In Chapter 5, we present a general discussion of the dissertation results, as integrated and compared across studies, and highlight potential directions for follow-up research.

Overview of the Dissertation Studies

Study 1: Portals to Frailty? Data-Driven Analyses Detect Early Frailty Subtypes

In this study (presented in Chapter 2; Bohn et al., 2021), we assembled data for a large sample of CN older adults (n = 649) from the VLS in order to test whether (a) early frailty profiles representing distinct configurations of aging morbidity could be empirically determined at baseline using person-centered and data-driven analytic technologies; (b) early frailty profiles were differentially related to level and change trajectories in a global frailty index and a latent neurocognitive speed variable; and (c) profile and prediction patterns generalized across sex. The impact of this study is identification of a complementary approach to frailty measurement and conceptualization that may be useful for early detection of elevated frailty risk.

Study 2: Tracking and Predicting Heterogenous Frailty Changes in Amnestic Mild Cognitive Impairment and Alzheimer's Disease: A Latent Transition Analysis

In this study (presented in Chapter 3), we advanced the results of Study 1 across a wider range of clinical cohorts, a different profile of measurement occasions, and a broad spectrum of morbidity indicators and predictors. Specifically, we assembled longitudinal big data from the

NACC for clinical cohorts of older adults with a baseline diagnosis of aMCI (baseline *n* = 878) or AD (baseline *n* = 2,196) in order to test the following specific research goals: (a) detect underlying clusters (or statuses) of aging multi-morbidity across two measurement occasions; (b) characterize patterns of frailty transitions; and (c) examine frailty emergence and progression in relation to demographic (age, sex, race/ethnicity, education), cognitive (clinical cohort, global cognition), and genetic (Apolipoprotein E) risk characteristics. Findings from this study advance the emerging literature on the natural history of frailty, data-driven frailty assessment, and frailty transitions in cognitive impairment and dementia.

Study 3: Application of Machine Learning Technology to the Identification of Frailty-Related Risk Characteristics that Discriminate Four COMPASS-ND Cohorts: Cognitively Normal, Subjective Cognitive Impairment, Mild Cognitive Impairment, and Alzheimer's Disease

This study (presented in Chapter 4) advanced the methodological approach of Studies 1 and 2 by (a) including a wider breadth of aging morbidity indicators, (b) examining the full AD spectrum with multiple clinical cohorts and (c) applying unbiased machine learning techniques to individual indicators (versus domains). The specific aims of this study were to: (a) apply machine learning technology to the analysis of COMPASS-ND data in order to test the relative predictive importance of 84 frailty-related features in discriminating older adults with SCI (*n* = 36), MCI (*n* = 116), or AD (*n* = 43) from a benchmark sample of CN controls (*n* = 60); (b) calculate a data-driven frailty index for each clinical cohort using data for the top 30 predictors identified in RF analysis; and (c) examine whether frailty levels varied across cohorts and complementary operationalizations of a frailty index. Findings from this study produced some resolution of the various empirical and clinical inconsistencies between leading frailty

operationalizations through a complementary conceptualization and the application of a data-driven approach to measurement, analysis, and interpretation.

Significance

Results from this line of research have important theoretical and practical applications. First, the dissertation studies supplement the small but growing body of research that has examined frailty measurement, analysis, and conceptualization from a data-driven and cohort specific perspective. These results have implications for clarifying selected contradictions or inconsistencies between prevailing frailty models and research approaches, and in turn, advancing understanding of the antecedents, emergence, or differential mechanisms associated with frailty. Second, in each of the dissertation studies, we identified data-driven clusters of characteristics or individual aging morbidity indicators that exacerbated risk for frailty emergence and progression and/or exacerbated cognitive decline, impairment, and dementia. Targeting and tracking these features in clinical-research settings may reduce the incidence of frailty and related negative outcomes across the AD spectrum.

Chapter 2: Study 1

Portals to Frailty? Data-Driven Analyses Detect Early Frailty Subtypes

---

Bohn, L., Zheng, Y., McFall, G. P., & Dixon, R. A. (2021). Portals to frailty? Data-driven analyses detect early frailty subtypes. *Alzheimer's Research & Therapy*, *13*(1), 1-12. https://doi.org/10.1186/s13195-020-00736-w

Background

Frailty is a heterogeneous condition that reflects accumulated age-related multi-morbidity, leading to diminished physical function and reduced physiological reserve (Morley et al., 2013). Progression along the fitness-frailty continuum is associated with an increased risk for numerous adverse aging outcomes (Romero-Ortuno & O'Shea, 2013), including differential cognitive decline, impairment, and dementia (Armstrong et al., 2015; Song et al., 2014; Thibeau et al., 2019). Against this backdrop, frailty is characterized as the most problematic expression of population aging (Clegg et al., 2013) and has been established as a priority area in clinical and research settings (Lim et al., 2018). Yet, considerable debate continues regarding the measurement and conceptualization of frailty. At present, two productive approaches dominate the literature: the physical frailty phenotype (Fried et al., 2001) and the frailty index (Mitnitski et al., 2001). We explored a third approach which could be applicable to early detection of elevated frailty risk: data-driven frailty assessment.

The physical phenotype approach defines frailty using the following cluster of variables: unintentional weight loss, self-reported exhaustion, weak grip strength, slow gait, and low physical activity. Notably, the phenotypes are ordered on the basis of the number of deficits, such that an individual with no deficits is classified as robust, one to two deficits is pre-frail, and three or more deficits is frail (Clegg et al., 2013). Because this approach incorporates a restricted number of physical characteristics, it may be limited in early detection of frailty risk. In contrast, the frailty index embraces heterogeneity in that responses across multiple indicators of aging systems are summed to create a single score that represents the ratio of deficits present in an individual relative to the total number of deficits considered. However, values on the index reflect the number of deficits that an individual has accumulated— and in pre-clinical aging, the global frailty index may

be relatively low while specific morbidity sources or domains of impairment are emerging. New data-driven analytic technologies may be useful in early detection of frailty profiles that serve as portals to the emergence of global frailty in aging— and as harbingers of a host of adverse aging outcomes.

Accordingly, we applied latent profile analysis (LPA) to a database of multi-morbidity indicators in order to detect underlying clusters or profiles of early frailty. LPA is a data-driven, person-centered statistical approach that can identify homogenous subgroups of individuals based on a set of observed indicators (Nylund-Gibson & Choi, 2018). This statistical approach is analogous to latent class analysis (LCA)— with the exception that the indicators are continuous. LPA is a sensitive analytical technique for studying heterogeneous clinical syndromes for which there is limited consensus on its defining and emergent characteristics (Muthén & Muthén, 2000). Findings from this study will advance the literature on measurement, analysis, and conceptualization of frailty by identifying empirically derived frailty profiles that are not differentiated on the basis of the number of physical impairments or proportion of accumulated deficits. Instead, detected profiles would reflect empirically observed classes of deficits, within a broad spectrum of morbidity, sharing pattern and severity characteristics.

Interestingly, identification of clusters of vulnerabilities, signs, and symptoms of frailty was established as a priority area in the beginning stages of this field (Bergman et al., 2007; Walston et al., 2006). Some experts reasoned that detection of frailty subtypes may contribute to a refined definition that would be useful for understanding the antecedents, emergence, or differential mechanisms associated with the variety of deficits subsumed under this general construct. Nevertheless, few studies have employed data-driven statistical techniques to distinguish frailty profiles based on multidomain deficit accumulation. Recently, Sadiq and colleagues (Sadiq et al.,

2018) assembled 18 items related to physical, functional, emotional, and social deficits and subjected these data to an LCA. Findings revealed three discrete frailty profiles that differed primarily in overall severity: (a) *not frail*, which was characterized by minimal impairment across all morbidity indicators, (b) *moderately frail*, which was characterized by moderate physical and functional limitations, and (c) *severely frail*, which was characterized by severe limitations in physical, functional, and emotional health. These findings converge with an earlier study that subjected 41 items related to self-reported health, cognitive function, social function, mental health, morbidity status, and functional limitations to an LCA (Looman et al., 2018). The following six frailty profiles, that also differed primarily in overall severity, were distinguished: *relatively healthy*, *mild physically frail*, *psychologically frail*, *severe physically frail*, *medically frail*, and *multi-frail*. The relatively healthy profile was characterized by minor problems across all indicators, whereas the remaining profiles were characterized by singular deficits in either physical or psychological health (at varying levels of severity), or by a combination of physical, psychological, cognitive, and social deficits.

We extend this prior work by determining which frailty profiles representing distinct configurations of aging morbidity are detected and examining how they are related to level and change trajectories in neurocognitive speed. Accumulating literature suggests that frailty and cognitive impairment are related but distinct concepts that frequently co-occur in older age (Robertson et al., 2013; Searle & Rockwood, 2015). Yet, few studies have examined broader definitions of frailty in relation to normal age-related decline in specific domains of cognition (Canevelli et al., 2015), such as neurocognitive speed (Boyle et al., 2010; Bunce et al., 2019; Rolfson et al., 2013). Given that non-memory domains may be particularly susceptible to early frailty effects (Wu et al., 2015), this is an important target of research attention. Findings from this

study may advance understanding of whether there are specific combinations of deficits that appear early in the frailty trajectory that predict an increased risk for accelerated cognitive decline.

Data were drawn from the Victoria Longitudinal Study (VLS), which is a multi-faceted, large-scale, long-term investigation of biomedical and neurocognitive aging (Dixon & de Frias, 2004). We assembled baseline data for each participant that included 50 items representing the typical heterogeneity of frailty (Thibeau et al., 2019). We used exploratory factor analysis to reduce the total number of items for estimation feasibility in the LPA. These results produced separable health domains that were interpreted on the basis of previous research (Kamaruzzaman et al., 2010; Lafortune et al., 2009; Sadiq et al., 2018). The proportion of deficits accumulated in each domain was calculated for each participant and used as continuous observed indicators in the LPA.

A recent VLS study used these same 50 items to calculate a frailty index and investigated whether the level and/or rate of change in frailty predicted performance and decline in neurocognitive speed across a 40-year band of aging (Thibeau et al., 2019). Findings showed that the level of frailty at baseline was predictive of neurocognitive speed performance at baseline. Moreover, change in the level of frailty was related to the rate of change in neurocognitive speed performance. Of note, these effects were moderated by sex, such that frailty change predicted the change in speed selectively for females, whereas frailty was unrelated to level or change in speed for males. At least one other study pointed to sex differences in the mechanisms linking frailty with early changes in cognitive function (Gifford et al., 2019). Given these findings and those from related research (McFall et al., 2019; Tierney et al., 2017), we tested whether our results were robust across sex.

The specific research goals (RG) of this study were as follows. For RG1, we employed LPA in order to detect empirically derived frailty profiles. As the sample was relatively healthy, we

expected to observe early frailty profiles that differed in the nature of deficit accumulation. For RG2, we investigated how frailty profiles related to performance and decline in neurocognitive speed. We expected to observe frailty-cognition associations, although the extent could vary across detected profiles. For RG3, we tested whether profile membership and trajectory predictions generalized across sex.

Methods

Participants

Participants were community dwelling older adults from the VLS who provided written and informed consent. Both the VLS and data collection procedures were in full and certified compliance with prevailing human research ethics guidelines and boards. The VLS is comprised of longitudinal cohorts that were aged 53–85 years at recruitment. Continuing participants were tested at an average of 4.4-year intervals. The source cohort for this study (n = 693) provided (a) baseline multi-morbidity data and (b) three waves of neurocognitive speed data. In accordance with established procedures for accelerated longitudinal designs (Galbraith et al., 2017; Little, 2013), age was used as the metric of longitudinal change. This approach allowed us to control for age-related effects and increase interpretability of the findings. The resulting design spans a 40-year band of aging (McFall et al., 2019).

The following exclusionary criteria were applied at baseline: (a) diagnosis of Alzheimer's or dementia (n = 0), (b) missing data across each of the 50 multi-morbidity items at baseline (n = 40), and (c) missing data across all waves and indicators of the latent speed variable (n = 4). Descriptive statistics for the remaining sample are outlined in Table 2-1 (n = 649; 431 females; Mage = 70.61, SD = 8.64, age range = 53 – 95 years; primarily White). Retention rates were 82% for wave 1 to wave 2 and 78% for wave 2 to wave 3.

Measures

Multi-morbidity data. We assembled baseline data for 50 multi-morbidity items that (a) have been used in the VLS and related research to form a frailty index (Thibeau et al., 2019), (b) have demonstrated associations with adverse brain and cognitive aging outcomes (Thibeau et al., 2019), and (c) satisfy prevailing conventions surrounding deficit accumulation approaches to frailty assessment (Searle et al., 2008). Data for these items were collected using self-report, physical examinations, and formal tests with standardized scales. All items were recoded such that scores ranged from 0 (no deficit present) to 1 (deficit was maximally expressed (Searle et al., 2008); see Table 2-2 for examples; full list in Supplementary Table 1, see Appendix A).

Neurocognitive speed. We represented neurocognitive speed as a multi-indicator latent variable using the following four manifest indicators: simple reaction time, choice reaction time, lexical decision, and sentence verification. Each of these indicators are multi-trial, computer-based neuropsychological tasks that have (a) established psychometric properties, (b) been widely used and documented in the VLS and related cognitive aging research, and (c) demonstrated sensitivity to neurocognitive factors and functional biomarkers (Bohn et al., 2020; Thibeau et al., 2019). The target measure for each task was the average response latency across the test trials. Responses were recoded such that higher scores represented better performance. We present descriptions of each task and data correction procedures in the Supplementary Methods (see Appendix A).

Statistical Analyses

Analyses were conducted using Mplus 8.0 (Muthén & Muthén, 1998-2017). Missing data were handled using full information maximum likelihood unless specified as otherwise.

Foundational analyses. The following foundational analyses served the purpose of testing and confirming basic characteristics of the neurocognitive speed data, as well as preparing the

latent variable: (a) confirmatory factor analysis, (b) longitudinal measurement invariance tests, and (c) unconditional latent growth modeling. Further details are presented in the Supplementary Methods (see Appendix A).

Focal analyses. The 50 multi-morbidity items were submitted to an exploratory factor analysis. Importantly, we made decisions related to the number of factors (health domains) and which indicators to retain on the basis of best-practices literature (Costello & Osborne, 2005; Muthén & Muthén, 2009). We verified that this latent structure fit the data using confirmatory factor analysis. Model fit was determined using standard indices (see Supplementary Methods, Appendix A).

For the latent profile analysis (LPA), we fit a sequence of models with varying numbers of latent profiles (e.g., 1, 2, 3). We selected the best fitting model based on interpretability of the study findings, as well as the following model parameters, tests, and fit indices (Masyn, 2012): (a) log-likelihood value (*LL*); (b) number of parameters estimated; (c) Bayesian Information Criterion (BIC); (d) sample-size adjusted BIC (SABIC); (e) Akaike Information Criterion (AIC); (f) adjusted Lo-Mendell-Rubin likelihood ratio test (LMR-LRT); (g) adjusted Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR-LRT); and (h) entropy. Low values of BIC, SABIC, and AIC indicate better fit (Nylund-Gibson & Choi, 2018). The LMR-LRT and VLMR-LRT compare the current model (*k*) against the model of one fewer latent profile (*k-1*); a non-significant *p*-value supports the selection of the *k-1* profile model (Nylund-Gibson & Choi, 2018). Entropy (ranging between 0 and 1) is not used for model selection but suggests the classification accuracy (the higher the better).

To avoid local maxima, we used 5000 multiple starting values. Indicators were allowed to covary within class, while the variances-covariances were constrained to be equal across profiles (i.e., class invariant-unrestricted structure). Alternative models allowing free estimation of

variance-covariance across profiles did not converge, suggesting over-parameterization (Chen et al., 2001). We controlled for potential age effects by regressing the observed indicators and profile membership on age. An adapted formula for Cohen's *d* was used to (a) calculate standardized mean differences across latent profiles in the observed indicators and (b) facilitate interpretations of the final latent-profile solution (Masyn, 2012). Values > 2.0 indicate a less than 20% overlap in profile-specific distributions and a high degree of separation on the associated indicator, whereas values < 0.85 indicate more than 50% overlap and a low degree of separation on the associated indicator.

We examined how the frailty profiles related to intercept (performance at a statistical centering age) and linear slope (longitudinal change) of neurocognitive speed using the manual BCH method (Asparouhov & Muthén, 2014; Vermunt, 2010). We tested whether latent profiles differed in the level or rate of change by comparing the nested models with constrained equal performance level (i.e., intercept) or decline in speed (i.e., linear slope) with the full model where performance level and decline in speed were freely estimated for each latent profile using χ^2 tests. Significant differences were inferred from a -2*LL* difference statistic (*D* at $p < .10$), which compared the unconstrained model to the constrained model.

We tested whether membership in the frailty profiles was comparable across sex by performing a multinomial logistic regression using the R3step approach (for further details see Asparouhov & Muthén, 2014). We examined whether frailty-cognition associations generalized across sex by regressing the intercept and slope of speed on sex separately for each profile.

Results

Foundational Analyses

Results of the confirmatory factor analysis indicated that a single-factor latent variable model for neurocognitive speed fit the data adequately. Measurement invariance tests showed full metric and full scalar invariance (final model fit indices: root mean square error of approximation (RMSEA) = .08; comparative fit index (CFI) = .96; standardized root mean square residual (SRMR) = .09; see Supplementary Table 2, Appendix A). Regarding the latent growth model for speed, participants demonstrated (a) significant variation in level of performance ($\widehat{\sigma}^2 = 1.00$, $p < .001$), (b) significant decline over time ($M = -.074$, $p < .001$), and (c) significant interindividual differences in the rate of decline ($\widehat{\sigma}^2 = .003$, $p < .001$; see Supplementary Table 3, Appendix A). This model was subsequently used to generate intercept and linear slope estimates for each participant, which then served as the target distal outcome measures.

RG1a: Exploratory and confirmatory factor analysis for multi-morbidity items

Results from the exploratory factor analysis indicated that a 7-factor solution adequately explained associations amongst the final 30 multi-morbidity items. We tested whether this latent structure fit the study data using confirmatory factor analysis. Results showed adequate to good model fit ($\chi^2(384) = 649.02$, $p < .001$; RMSEA = .03; CFI = .90) and all indicators had strong loadings on the corresponding latent construct (for model depiction see Supplementary Figure 1, Appendix A). In accordance with earlier research (Kamaruzzaman et al., 2010; Lafortune et al., 2009; Sadiq et al., 2018), we labeled these domains as: mobility ($n = 4$), instrumental health ($n = 6$), emotional wellbeing ($n = 4$), comorbidity ($n = 4$), respiratory symptoms ($n = 3$), cardiac symptoms ($n = 5$), and physical activity ($n = 4$). Indicators for each domain are outlined in Table 2-2. We subsequently calculated the proportion of deficits in each domain for each participant. Values ranged between 0 and 1, with higher scores denoting greater impairment. These data were used as continuous observed indicators in the LPA.

RG1b: Identification of latent frailty profiles

As shown in Table 2-3, AIC, BIC, and SABIC all steadily decreased (i.e., became more negative) as the number of latent profiles increased, suggesting that model fit improved with the addition of each latent profile. Further, the adjusted LMR-LRT ($p < .001$) and VLMR-LRT ($p < .001$) indicated that the 3-profile solution provided better fit relative to the 2-profile solution. Notably, prevalence of each profile exceeded a conventional standard of 5% (Nylund-Gibson & Choi, 2018). Entropy for this solution was also high (0.99), indicating that participants were classified into the profiles with a high degree of precision. The 3-profile solution was therefore selected as the final model.

Interpretation of the frailty profiles. Model estimated indicator means for each latent profile are depicted in Figure 2-1. The first profile ($n = 542$, 84%) was characterized by relatively low impairment across all observed indicators and was thus labeled as *not-clinically-frail* (NCF). Notably, participants in this profile had an average score on the frailty index (see Table 2-1) that fell below the clinical threshold typically used to assign frailty status, whereas the remaining two profiles had scores that met or exceeded a previously established cut-off value of .20 (Searle et al., 2008). The second profile ($n = 59$, 9%) was characterized by pronounced impairment in mobility function relative to the first ($d = 5.09$) and third ($d = 3.90$) profile. This profile was thus labeled as *mobility-type frailty* (MTF). The third profile ($n = 48$, 7%), labeled as *respiratory-type frailty* (RTF), was characterized by pronounced impairment in respiratory function relative to the NCF ($d = 6.96$) and MTF profiles ($d = 4.72$). Interestingly, none of these profiles were distinguished on the basis of emotional well-being, comorbidity, cardiac symptoms, or physical activity (for details see Supplementary Table 4, Appendix A). As highlighted in Table 2-1, the pattern of mean differences observed across profiles in performance-based tasks was in keeping with our interpretations. That

is, participants classified into MTF had the slowest performance on a timed-walk task, while participants classified into RTF had the lowest peak-expiratory flow. We present further descriptive baseline information for each latent profile in Table 2-1.

In a series of follow-up analyses, we tested whether the MTF and RTF profiles function as morbidity-intensive portals that subgroups of older adults pass through into classifiable chronic frailty. We assembled three waves of data for the 50-item frailty index (Thibeau et al., 2019) and calculated a growth model over the 40-year longitudinal band. Key results showed significant (a) variation in the level of frailty ($\widehat{\sigma}^2 = .004$, $p < .001$), (b) increase in frailty over time ($M = .003$, $p < .001$), and (c) interindividual differences in the rate of frailty progression ($\widehat{\sigma}^2 = .001$, $p < .001$; see Supplementary Table 3, Appendix A). We generated intercept and linear slope estimates for each participant and tested whether the profiles were differentially related to level (severity) and rate of change in the frailty index using the manual BCH approach. Evidence in support of a portal approach to frailty emergence and progression would be constituted by a higher level and steeper rate of deficit accumulation for MTF and RTF as compared to the NCF profile.

Results for portal-related analyses. The predicted growth curve model for the frailty index is presented in Figure 2-2. Consistent with our expectations, profiles differed significantly in intercept. Specifically, older adults with MTF ($b = .20$, $p < .001$) and RTF ($b = .20$, $p < .001$) had higher (worse) scores on the frailty index relative to those who were NCF ($b = .14$, $p < .001$; $D = 11.20$, $\Delta df = 4$, $p < .001$). Differences across profiles in the rate of frailty progression (slope) were also in the expected direction. MTF was associated with the fastest rate of deficit accumulation ($b = .005$, $p < .001$), followed in order by RTF ($b = .004$, $p < .001$; $D = 8.62$, $\Delta df = 2$, $p = .01$), and then NCF ($b = .003$, $p < .001$; $D = 14.71$, $\Delta df = 2$, $p < .001$).

RG2: Latent profile-speed associations

The predicted growth curve model for neurocognitive speed is depicted in Figure 2-3. Intercept did not vary significantly across MTF (b = -.46, p < .001), RTF (b = -.47, p < .001), and NCF (b = -.24, p < .001) profiles (D = 7.87, Δdf = 4, p = .10). However, we observed significant differences across profiles in the rate of cognitive decline (slope; D = 31.81, Δdf = 4, p < .001). Specifically, MTF (b = -.10, p < .001) was associated with more precipitous decline relative to RTF (b = -.08, p < .001; D = 13.90, Δdf = 2, p < .001) and the NCF profile (b = -.08, p < .001; D = 23.61, Δdf = 2, p < .001). RTF was also associated with more accelerated decline relative to the NCF profile (D = 7.88, Δdf = 2, p = .02).

RG3: Generalizability of profile membership and prediction patterns across sex

We found that profile membership was similar across sex (coded as 0 = female, 1 = male) such that male sex was equally related to the likelihood of being classified into MTF (OR = .62, *ns*) or RTF (OR = 0.61, *ns*) as compared to NCF. Further, male sex was equally related to the likelihood of being classified into RTF as compared to MTF (OR = .98, *ns*). Similarly, sex showed comparable associations with the level and rate of change in neurocognitive speed for each of the frailty profiles (all p-values > .20).

Discussion

The frailty phenotype (Fried et al., 2001) and the frailty index (Mitnitski et al., 2001) are the two important and productive approaches to measuring, conceptualizing, and investigating frailty. Each of these approaches have been widely used to capture variations in the risk for adverse aging outcomes (Gonzalez-Colaço Harmand et al., 2017), including accelerated cognitive decline and dementia (Armstrong et al., 2015; Song et al., 2014). The present study examined a complementary approach that relied on data-driven statistical techniques. Specifically, we submitted 50 items to an exploratory factor analysis and derived the following 7 domains of aging morbidity: mobility,

instrumental health, emotional wellbeing, comorbidity, respiratory symptoms, cardiac symptoms, and physical activity (Kamaruzzaman et al., 2010; Lafortune et al., 2009; Sadiq et al., 2018). We calculated the proportion of deficits accumulated in each domain and submitted these data to a latent profile analysis (LPA) in order to detect frailty profiles. We then examined whether (a) distinguishable early frailty profiles could be empirically detected and characterized, (b) frailty profiles differentially predicted the level and rate of change in neurocognitive speed, and (c) profile membership and prediction of cognitive trajectories was comparable across sex.

RG1: Identification of latent frailty profiles

In this person-centered analysis, three mutually exclusive early morbidity profiles of individuals were identified. The first profile we identified, *not-clinically-frail* (NCF), has been reliably documented in related research (Liu et al., 2017; Looman et al., 2018; Olaya et al., 2017; Sadiq et al., 2018) and was characterized by individuals with minimal impairment across the observed indicators and low scores on the frailty index. This pattern would be expected in a relatively healthy and cognitively normal aging group, and thus would include numerous persons who could later develop global or phenotypic frailty. The second profile, *mobility-type frailty* (MTF), was differentiated on the basis of deficits in mobility function. This profile is consistent with some research that suggests mobility deficits may aggregate to form a unique frailty subtype (Chhetri et al., 2017; Sarksian et al., 2008; Sourial et al., 2012). For example, Liu and colleagues (Liu et al., 2017) recently applied latent class analysis (LCA) to the five items from the physical frailty phenotype and detected four subtypes, one of which was labelled *mobility-type*. The present study extracts this subtype from a much broader range of morbidity measures and identifies it as an early frailty profile. The third profile we detected represented *respiratory-type frailty* (RTF). This profile was comprised of individuals with pronounced impairment in respiratory function.

Identification of RTF as an early frailty profile advances the literature on subgroups of frail older adults. Although expanding (Nguyen et al., 2019), the vast majority of available works have conceptualized frailty using only the physical phenotype (Bandeen-Roche et al., 2006; Liu et al., 2017; Lohman et al., 2014; Segaux et al., 2019) or have not included respiratory symptoms and diseases in the measurement of aging morbidity (Looman et al., 2018; Sadiq et al., 2018). However, another recent study also distinguished a data-driven frailty subtype marked by concomitant respiratory impairment (Pikoula et al., 2019). Our results suggests that deficits in respiratory function are a defining characteristic of early frailty profiles and should be targeted and tracked in clinical and research settings (Olaya et al., 2017; Sugimoto et al., 2020; Trevisan et al., 2019). Finally, we note that older adults classified into the two early frailty profiles had comparable scores on the 50-item frailty index— and these scores exceeded those of the non-frail group and met an established threshold for clinical frailty (Searle et al., 2008).

We tested whether MTF and RTF may represent early and specific morbidity-intensive portals into broader and chronic frailty in a series of follow-up analyses. Notably, the results buttressed this interpretation. Not only did older adults classified as MTF or RTF have higher levels of frailty (intercept), but they also showed more rapid progression into general frailty as compared to those who were NCF (slope). Interestingly, MTF was also associated with a faster rate of deficit accumulation as compared to RTF. These findings contribute to the emerging literature on trajectories of frailty (Rohrmann, 2020) and extend earlier research that reported single indicators of mobility (Doi et al., 2018; Fallah et al., 2011) and respiratory function (Pollack et al., 2017; Vaz Fragoso et al., 2012) are predictive of frailty progression. We advance these works by proposing and validating a portal approach to frailty emergence, which reasons that profiles of aging morbidity marked by mobility or respiratory deficits may serve as gateways to classifiable

global frailty, which then cascades into more rapid and widespread deficit accumulation (Anstey & Dixon, 2014). The present focus on detecting early manifestations of frailty profiles and the representation of these as portals into global frailty is a promising research direction. Future epidemiological studies would profitably be directed towards replicating and extending these results (e.g., data-driven frailty assessment in clinical cohorts).

RG2: Latent profile-speed associations

We found that, while the two emergent frailty profiles differed only marginally for prediction of level (intercept of neurocognitive speed), they differed significantly for slope (decline or slowing). Regarding level, the pattern of effects was in the expected direction (Bunce et al., 2019; Rolfson et al., 2013; Thibeau et al., 2019). Specifically, older adults classified into MTF or RTF subtypes trended towards worse performance relative to those who were NCF. Notably, regarding slope, older adults classified as having MTF showed the most precipitous decline, followed in order by RTF and then NCF. These relationships support the validity of these profiles and suggest that distinct configurations of aging morbidity marked by deficits in mobility and respiratory function may have differential effects on neurocognitive slowing. We note that these results cannot be attributed to age, educational background, or proportion of deficits accumulated. Three reasons are noted. First, we statistically controlled for the effects of age. Second, the frailty profiles did not differ from one another in their level of educational achievement. Third, participants assigned to MTF and RTF had comparable baseline scores (and intercept values) on the frailty index and yet they differed in the rate of decline.

To our knowledge, this is the first study to determine data-driven early frailty profiles using LPA and examine their prediction of cognitive aging trajectories. Of the related works summarized above, cognition was treated variably as (a) a study covariate (Lohman et al., 2014), (b) amongst

one of the indicators of aging morbidity (Looman et al., 2018; Segaux et al., 2019), or (c) not relevant or included in the analysis (Bandeen-Roche et al., 2006; Sadiq et al., 2018). Notably, Liu and colleagues (2017) explored descriptive differences across frailty subtypes and reported findings that run in parallel to our own in mobility-type frailty was associated with lower scores on the MMSE relative to the robust subtype. Other research highlights that single indicators of mobility or physical function, such as gait speed or grip strength, are associated with decline in processing speed (Hooghiemstra et al., 2017; Inzitari et al., 2007). Far less research has examined respiratory-cognition associations (Duggan et al., 2018), particularly within the context of frailty (Vaz Fragoso et al., 2012). Olaya and colleagues (2017) recently reported that older adults assigned to a *cardiorespiratory* latent multi-morbidity profile had worse verbal memory performance relative to a *healthy* profile. Several recent reviews have also reported that single indicators of respiratory function, such as forced expiratory volume or asthma, predict neurocognitive slowing (Dodd, 2015; Duggan et al., 2018). Nevertheless, this is the first study to extract MTF and RTF profiles from a multi-morbidity inventory in mostly non-frail older adults and then systematically compare them in their initial frailty scores (similar), rate of frailty progression (dissimilar), and their predictions of cognitive change trajectories (dissimilar). These results suggest older adults presenting with deficits in mobility or respiratory function may be particularly vulnerable to advancing frailty and accelerated neurocognitive slowing. Proper assessment and management of these signs, symptoms, and diseases as they appear early on in the frailty trajectory is therefore encouraged. Accumulating literature suggests that frailty is a potentially reversible condition (Canevelli et al., 2017). It has therefore been reasoned that early interventions designed to reverse or attenuate frailty progression may have downstream effects on reducing negative aging

outcomes, including differential cognitive decline and impairment (Borges et al., 2019; Robertson et al., 2013).

RG3: Generalizability of profile membership and prediction patterns across sex

Limited research has examined whether data-driven early frailty profiles, particularly those derived on the basis of multidomain deficit accumulation, are robust across sex. A small number of studies have explored whether the proportion of males and females assigned into frailty profiles is comparable; however, this question differs conceptually from the one tested in the present study and the earlier findings were equivocal (Liu et al., 2017; Sadiq et al., 2018; Segaux et al., 2019). Our results indicated that males and females were equally likely to be classified into the MTF, RTF, and NCF profiles. Looman and colleagues (2018) also examined whether profile membership generalized across sex and reported findings that converge with our own. Previous literature suggests that there may be sex differences in the impact of frailty on cognitive aging trajectories (Gifford et al., 2019; Song et al., 2014; Thibeau et al., 2019). However, we did not detect such a pattern in our data. Rather, we found that performance and decline in neurocognitive speed was comparable across sex. Sex differences may be more likely to appear in later life or in more serious frailty conditions.

Given the heterogeneity of frailty, the mechanisms underlying the observed associations are unclear. Current reviews attribute frailty-cognition associations to hormonal dysregulation, nutritional factors and deficiencies, chronic inflammation, and cardiovascular risks (Canevelli et al., 2015; Panza et al., 2015; Robertson et al., 2013). Perhaps more relevant for the present research are studies showing that non-demented older adults accumulate neuropathology (Buchman et al., 2008, 2013; Wolf et al., 1999) and show structural and functional declines (Seidler et al., 2010) in the regions that underlie motor functions and processing speed, such as the striatum, substantia

nigra, and motor cortices. Increased white matter hyper-intensities and decreased cerebellar gray matter volumes have also been linked with reduced mobility function (Chhetri et al., 2017) and poorer performance on speeded tasks (Eckert et al., 2010; Papp et al., 2014). Similarly, impaired respiratory function predicts overall and subcortical brain atrophy as well as white matter hyperintensities (Sachdev et al., 2006). One possible explanation for the finding that MTF was associated with accelerated cognitive decline relative to RTF is that our measures of neurocognitive speed were computer-based reaction time tasks. Performance on these tasks thus reflects not only processing speed, but also motor control and muscle function. Individuals with deficits in mobility function may therefore have been disproportionately impaired on these tasks relative to those with respiratory deficits. Although linked to relevant literature, these explanations are speculative and multiple contributing mechanisms likely account for the frailty-speed associations. Continued research efforts are required in order to understand the pathophysiologic underpinnings of MTF and RTF.

Strengths and limitations

We acknowledge several methodological strengths and limitations. First, with respect to the former, we used a substantial and well-characterized sample of participants from the VLS. These individuals were tested on three occasions across a 40-year band of aging and were relatively healthy and free of neurodegenerative disease at baseline. These characteristics allowed us to distinguish and subsequently examine the impact of early frailty profiles on normal cognitive aging trajectories. At the same time, our findings may be limited in generalizability to other populations (e.g., more frail older adults; ethnic minorities) or contexts (e.g., continuing care settings). Future investigations should explore this possibility. Second, we examined our research questions using contemporary statistical approaches. Specifically, we derived empirically based frailty profiles

using LPA. This data-driven approach boasts several advantages over classical statistical models (e.g., cluster analysis; Muthén & Muthén, 2000), such as model-based participant classifications, statistical diagnostic tools that elucidate the quality of participant classifications, and information-theoretic indices that favor selection of the most parsimonious model (thus discouraging overfitting). We validated our profiles by examining how they related to the level and rate of change in frailty and neurocognitive speed using the BCH approach, which allowed us to statistically account for misclassification errors. We calculated the primary distal outcome measure using multiple standard neuropsychological tasks, which contributed to a validated, invariant, longitudinal, latent measure of neurocognitive speed. We controlled for the potential confounding effects of age, as well as verified that prediction patterns generalized across sex and could not be attributed to educational background or proportion of deficits accumulated. Third, we assembled baseline data that represented the heterogeneity of frailty. This enabled us to detect nuanced frailty profiles and address a prominent criticism of earlier data-driven research (Rockwood et al., 2007). It is worth noting, however, that our indicators in the LPA do not represent the full range of deficits that older adults may accumulate. For example, due to unavailability, we did not include indicators related to social function (beyond those included in instrumental health) or nutritional status. Previous studies including these indicators did not distinguish social or nutrition profiles (Looman et al., 2018; Sadiq et al., 2018; Segaux et al., 2019; Sourial et al., 2012). This is a common issue in frailty research. The phenotype approach does not include all possible phenotypes and the frailty index includes no phenotypes, but rather a score that could vary according to the available items. Nevertheless, future studies could explore whether inclusion of social and nutritional deficits may result in profile interpretations and prediction patterns that diverge from the present research.

Conclusions

Our study distinguished three early frailty profiles using data-driven statistical techniques: not-clinically-frail (NCF), mobility-type frailty (MTF), and respiratory-type frailty (RTF). Whereas the former and larger profile represented older adults with minimal current impairment across multiple indicators of aging morbidity, the latter two profiles represented individuals with marked impairment in either mobility or respiratory function. Prevailing approaches that collapse across markers of aging morbidity may therefore mask important variability, including identification of (a) differentiable profiles that may be characterized as morbidity-intensive portals into broader and chronic frailty and (b) older adults at risk for accelerated cognitive decline and impairment. These profiles were differentially associated with longitudinal change in neurocognitive slowing, such that MTF was associated with the steepest decline, followed by RTF. As new and more effective treatments become available, studies directed towards identifying subgroups of frail older adults who are not yet exhibiting cognitive impairment but who are at increased risk are essential. Our results indicate that older adults presenting with mobility or respiratory complaints may benefit from early and targeted interventions (Apóstolo et al., 2018; Sugimoto et al., 2020). Future research should explore the extent to which rehabilitation and pharmacologic treatments targeting these deficits may offset or delay cognitive decline and frailty progression.

References

Anstey, K. J., & Dixon, R. A. (2014). Applying a cumulative deficit model of frailty to dementia: Progress and future challenges. *Alzheimer's Research & Therapy*, *6*(84), 1–3. https://doi.org/http://alzres.com/content/6/9/84

Apóstolo, J., Cooke, R., Bobrowicz-Campos, E., Santana, S., Marcucci, M., Cano, A., Vollenbroek-Hutten, M., Germini, F., D'Avanzo, B., Gwyther, H., & Holland, C. (2018). Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports*, *16*(1), 140–232. https://doi.org/10.11124/JBISRIR-2017-003382

Armstrong, J. J., Mitnitski, A., Andrew, M. K., Launer, L. J., White, L. R., & Rockwood, K. (2015). Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: a multistate modeling approach. *Alzheimer's Research and Therapy*, *7*(38), 1–9. https://doi.org/10.1186/s13195-015-0120-7

Asparouhov, T., & Muthén, B. (2014a). Auxiliary variables in mixture modeling: Three-step approaches using Mplus. *Structural Equation Modeling: A Multidisciplinary Journal*, *21*(3), 329–341. https://doi.org/10.1080/10705511.2014.915181

Asparouhov, T., & Muthén, B. O. (2014b). Auxiliary variables in mixture modeling: using the BCH method in Mplus to estimate a distal outcome model and an arbitrary second model. *Mplus Web Notes*, *21*, 1–22.

Bandeen-Roche, K., Xue, Q. L., Ferrucci, L., Walston, J., Guralnik, J. M., Chaves, P., Zeger, S. L., & Fried, L. P. (2006). Phenotype of frailty: Characterization in the Women's Health and Aging Studies. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61A*(3), 262–266. https://doi.org/10.1093/gerona/61.3.262

Bergman, H., Ferrucci, L., Guralnik, J., Hogan, D. B., Hummel, S., Karunananthan, S., & Wolfson, C. (2007). Frailty: An emerging research and clinical paradigm—issues and controversies. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(7), 731–737. https://doi.org/10.1093/gerona/62.7.731

Bohn, L., McFall, G. P., Wiebe, S. A., & Dixon, R. A. (2020). Body mass index predicts cognitive aging trajectories selectively for females: evidence from the Victoria Longitudinal Study. *Neuropsychology*, *34*(4), 388–403. https://doi.org/10.1037/neu0000617

Borges, M. K., Canevelli, M., Cesari, M., & Aprahamian, I. (2019). Frailty as a predictor of cognitive disorders: A systematic review and meta-analysis. *Frontiers in Medicine*, *6*(26), 1–8. https://doi.org/10.3389/fmed.2019.00026

Boyle, P., Buchman, A. S., Wilson, R. S., Leurgans, S. E., & Bennett, D. A. (2010). Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *Journal of the American Geriatrics Society*, *58*(2), 248–255. https://doi.org/doi:10.1111/j.1532-5415.2009.02671.x

Buchman, A. S., Schneider, J. A., Leurgans, S., & Bennett, D. A. (2008). Physical frailty in older persons is associated with Alzheimer disease pathology. *Neurology*, *71*(7), 499–504. https://doi.org/10.1212/01.wnl.0000324864.81179.6a

Buchman, A. S., Yu, L., Wilson, R. S., Schneider, J. A., & Bennett, D. A. (2013). Association of brain pathology with the progression of frailty in older adults. *Neurology*, *80*(22), 2055–2061. https://doi.org/10.1212/WNL.0b013e318294b462

Bunce, D., Batterham, P. J., & Mackinnon, A. J. (2019). Long-term associations between physical frailty and performance in specific cognitive domains. *Journals of Gerontology Series B:*

Psychological Sciences and Social Sciences, *74*(6), 919–926. https://doi.org/10.1093/geronb/gbx177

Canevelli, M., Bruno, G., Remiddi, F., Vico, C., Lacorte, E., Vanacore, N., & Cesari, M. (2017). Spontaneous reversion of clinical conditions measuring the risk profile of the individual: From frailty to mild cognitive impairment. *Frontiers in Medicine*, *4*(184), 1–6. https://doi.org/10.3389/fmed.2017.00184

Canevelli, M., Cesari, M., & van Kan, G. A. (2015). Frailty and cognitive decline: How do they relate? *Current Opinion in Clinical Nutrition and Metabolic Care*, *18*, 43–50. https://doi.org/10.1097/MCO.0000000000000133

Chen, F., Bollen, K. A., Paxton, P., Curran, P. J., & Kirby, J. B. (2001). Improper solutions in structural equation models. *Sociological Methods & Research*, *29*(4), 468–508.

Chhetri, J. K., Chan, P., Vellas, B., & Cesari, M. (2017). Motoric cognitive risk syndrome: Predictor of dementia and age-related negative outcomes. *Frontiers in Medicine*, *4*(166), 1–8. https://doi.org/10.3389/fmed.2017.00166

Clegg, A., Young, J., Iliffe, S., Olde Rikkert, M. G. M., & Rockwood, K. (2013). Frailty in older people. *Lancet*, *381*(9868), 752–762. https://doi.org/10.1016/S0140-6736(12)62167-9

Costello, A. B., & Osborne, J. W. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research & Evaluation*, *10*(7), 1–9.

Dixon, R. A., & de Frias, C. M. (2004). The Victoria Longitudinal Study: From characterizing cognitive aging to illustrating changes in memory compensation. *Aging, Neuropsychology, and Cognition*, *11*(2), 346–376. https://doi.org/https://doi.org/10.1080/13825580490511161

Dodd, J. W. (2015). Lung disease as a determinant of cognitive decline and dementia. *Alzheimer's Research and Therapy*, *7*(32), 1–8. https://doi.org/10.1186/s13195-015-0116-3

Doi, T., Makizako, H., Tsutsumimoto, K., Nakakubo, S., Kim, M. J., Kurita, S., Hotta, R., & Shimada, H. (2018). Transitional status and modifiable risk of frailty in Japanese older adults: A prospective cohort study. *Geriatrics & Gerontology International*, *18*(11), 1562–1566. https://doi.org/10.1111/ggi.13525

Duggan, E. C., Graham, R. B., Piccinin, A. M., Jenkins, N. D., Clouston, S., Muniz-Terrera, G., & Hofer, S. M. (2018). Systematic review of pulmonary function and cognition in aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *XX*(XX), 1–16. https://doi.org/10.1093/geronb/gby128

Eckert, M. A., Keren, N. I., Roberts, D. R., Calhoun, V. D., & Harris, K. C. (2010). Age-related changes in processing speed: Unique contributions of cerebellar and prefrontal cortex. *Frontiers in Human Neuroscience*, *4*(10), 1–14. https://doi.org/10.3389/neuro.09.010.2010

Fallah, N., Mitnikski, A., Searle, S. D., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2011). Transitions in frailty status in older adults in relation to mobility: a multi-state modeling approach employing a deficit count. *Journal of the American Geriatrics Society*, *59*(3), 524–529. https://doi.org/10.1016/j.biotechadv.2011.08.021.Secreted

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., Burke, G., & McBurnie, M. A. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56A*(3), M146–M156. https://doi.org/10.1093/gerona/56.3.M146

Galbraith, S., Bowden, J., & Mander, A. (2017). Accelerated longitudinal designs: An overview of modelling, power, costs and handling missing data. *Statistical Methods in Medical Research*, *26*(1), 374–398. https://doi.org/10.1177/0962280214547150

Gifford, K. A., Bell, S. P., Liu, D., Neal, J. E., Turchan, M., Shah, A. S., & Jefferson, A. L. (2019). Frailty is related to subjective cognitive decline in older women without dementia. *Journal of the American Geriatrics Society*, *67*(9), 1803–1811. https://doi.org/10.1111/jgs.15972

Gonzalez-Colaço Harmand, M., Meillon, C., Bergua, V., Tabue Teguo, M., Dartigues, J. F., Avila-Funes, J. A., & Amieva, H. (2017). Comparing the predictive value of three definitions of frailty: Results from the Three-City study. *Archives of Gerontology and Geriatrics*, *72*, 153–163. https://doi.org/10.1016/j.archger.2017.06.005

Hooghiemstra, A. M., Ramakers, I. H. G. B., Sistermans, N., Pijnenburg, Y. A. L., Aalten, P., Hamel, R. E. G., Melis, R. J. F., Verhey, F. R. J., Olde Rikkert, M. G. M., Scheltens, P., & van der Flier, W. M. (2017). Gait speed and grip strength reflect cognitive impairment and are modestly related to incident cognitive decline in memory clinic patients with subjective cognitive decline and mild cognitive impairment: Findings from the 4C study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *72*(6), 846–854. https://doi.org/10.1093/gerona/glx003

Inzitari, M., Newman, A. B., Yaffe, K., Boudreau, R., De Rekeneire, N., Shorr, R., Harris, T. B., & Rosano, C. (2007). Gait speed predicts decline in attention and psychomotor speed in older adults: The Health Aging and Body Composition study. *Neuroepidemiology*, *29*, 156–162. https://doi.org/10.1159/000111577

Kamaruzzaman, S., Ploubidis, G. B., Fletcher, A., & Ebrahim, S. (2010). A reliable measure of frailty for a community dwelling older population. *Health and Quality of Life Outcomes*, *8*(123), 1–14. https://doi.org/10.1186/1477-7525-8-123

Lafortune, L., Béland, F., Bergman, H., & Ankri, J. (2009). Health status transitions in community-living elderly with complex care needs: A latent class approach. *BMC Geriatrics*, *9*(6), 1–14. https://doi.org/10.1186/1471-2318-9-6

Lim, W.-S., Canevelli, M., & Cesari, M. (2018). Editorial: Dementia, frailty and aging. *Frontiers in Medicine*, *5*(168), 1–3. https://doi.org/10.3389/fmed.2018.00168

Little, T. D. (2013). *Longitudinal structural equation modeling*. Guilford Press.

Liu, L. K., Guo, C. Y., Lee, W. J., Chen, L. Y., Hwang, A. C., Lin, M. H., Peng, L. N., Chen, L. K., & Liang, K. Y. (2017). Subtypes of physical frailty: Latent class analysis and associations with clinical characteristics and outcomes. *Scientific Reports*, *7*(46417), 1–9. https://doi.org/10.1038/srep46417

Lohman, M., Dumenci, L., & Mezuk, B. (2014). Sex differences in the construct overlap of frailty and depression: Evidence from the Health and Retirement Study. *Journal of the American Geriatrics Society*, *62*(3), 500–505. https://doi.org/10.1111/jgs.12689

Looman, W. M., Fabbricotti, I. N., Blom, J. W., Jansen, A. P. D., Lutomski, J. E., Metzelthin, S. F., & Huijsman, R. (2018). The frail older person does not exist: Development of frailty profiles with latent class analysis. *BMC Geriatrics*, *18*(84), 1–11. https://doi.org/10.1186/s12877-018-0776-5

Masyn, K. E. (2012). Latent class analysis and finite mixture modeling. In T. D. Little (Ed.), *The Oxford Handbook of Quantitative Methods* (2nd ed., pp. 551–611). Oxford University Press.

McFall, G. P., McDermott, K. L., & Dixon, R. A. (2019). Modifiable risk factors discriminate memory trajectories in non-demented aging: Precision factors and targets for promoting healthier brain aging and preventing dementia. *Journal of Alzheimer's Disease*, *70*(s1), S101–S118. https://doi.org/10.3233/JAD-180571

Mitnitski, A. B., Molinger, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *The Scientific World*, *1*, 323–336. https://doi.org/10.1100/tsw.2001.58

Morley, J. E., Vellas, B., Abellan van Kan, G., Anker, S. D., Bauer, J. M., Bernabei, R., Cesari, M., Chumlea, W. C., Doehner, W., Evans, J., Fried, L. P., Guralnik, J. M., Katz, P. R., Malmstrom, T. K., McCarter, R. J., Robledo, L. M. G., Rockwood, K., Haehling, S. v., Vandewoude, M. F., & Walston, J. (2013). Frailty consensus: A call to action. *Journal of American Medical Directors Association*, *14*(6), 392–397. https://doi.org/10.1016/j.jamda.2013.03.022

Muthén, B. O., & Muthén, L. K. (2000). Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcoholism: Clinical and Experimental Research*, *24*(6), 882–891. https://doi.org/10.1111/j.1530-0277.2000.tb02070.x

Muthén, L. K., & Muthén, B. O. (2009). *Mplus short courses topic 1: Exploratory factor analysis, confirmatory factor analysis, and structural equation modeling for continuous outcomes*. Muthén & Muthén. http://www.statmodel.com/course_materials.shtml

Muthén, L. K., & Muthén, B. O. (2017). *Mplus user's guide. Eigth Edition.* Muthén & Muthén.

Nguyen, Q. D., Wu, C., Odden, M. C., & Kim, D. H. (2019). Multimorbidity patterns, frailty, and survival in community-dwelling older adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *74*(8), 1265–1270. https://doi.org/10.1093/gerona/gly205

Nylund-Gibson, K., & Young, A. C. (2018). Ten frequently asked questions about latent class analysis. *Translational Issues in Psychological Science*, *4*(4), 440–461. https://doi.org/http://dx.doi.org/10.1037/tps0000176

Olaya, B., Moneta, M. V., Caballero, F. F., Tyrovolas, S., Bayes, I., Ayuso-Mateos, J. L., & Haro, J. M. (2017). Latent class analysis of multimorbidity patterns and associated outcomes in Spanish older adults: A prospective cohort study. *BMC Geriatrics*, *17*, 1–10. https://doi.org/10.1186/s12877-017-0586-1

Panza, F., Solfrizzi, V., Barulli, M. R., Santamato, A., Seripa, D., Pilotto, A., & Logroscino, G. (2015). Cognitive frailty: A systematic review of epidemiological and neurobiological evidence of an age-related clinical condition. *Rejuvenation Research*, *18*(5), 389–412. https://doi.org/10.1089/rej.2014.1637

Papp, K. V., Kaplan, R. F., Springate, B., Moscufo, N., Wakefield, D. B., Guttmann, C. R. G., & Wolfson, L. (2014). Processing speed in normal aging: Effects of white matter hyperintensities and hippocampal volume loss. *Neuropsychology, Development, and Cognition: Section B, Aging, Neuropsychology, and Cognition*, *21*(2), 197–213. https://doi.org/10.1080/13825585.2013.795513

Pikoula, M., Quint, J. K., Nissen, F., Hemingway, H., Smeeth, L., & Denaxas, S. (2019). Identifying clinically important COPD sub-types using data-driven approaches in primary care population based electronic health records. *BMC Medical Informatics and Decision Making*, *19*(86), 1–14. https://doi.org/10.1186/s12911-019-0805-0

Pollack, L. R., Harrison, S. L., Cawthon, P. M., Ensrud, K., Lane, N. E., Barrett-Connor, E., & Dam, T. T. (2017). Patterns and predictors of frailty transitions in older men: The

Osteoporotic Fractures in Men study. *Journal of the American Geriatrics Society*, *65*(11), 2473–2479. https://doi.org/10.1111/jgs.15003

Robertson, D. A., Savva, G. M., & Kenny, R. A. (2013). Frailty and cognitive impairment— A review of the evidence and causal mechanisms. *Ageing Research Reviews*, *12*, 840–851. https://doi.org/10.1016/j.arr.2013.06.004

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62A*(7), 738–743. https://doi.org/10.1093/gerona/62.7.738

Rohrmann, S. (2020). Epidemiology of frailty in older people. *Advances in Experimental Medicine and Biology*, *1216*, 21–27. https://doi.org/10.1007/978-3-030-33330-0_3

Rolfson, D. B., Wilcock, G., Mitnitski, A., King, E., De Jager, C. A., Rockwood, K., Fallah, N., & Searle, S. D. (2013). An assessment of neurocognitive speed in relation to frailty. *Age and Ageing*, *42*(2), 191–196. https://doi.org/10.1093/ageing/afs185

Romero-Ortuno, R., & O'Shea, D. (2013). Fitness and frailty: Opposite ends of a challenging continuum! Will the end of age discrimination make frailty assessments an imperative? *Age and Ageing*, *42*, 279–280. https://doi.org/10.1093/ageing/afs189

Sachdev, P. S., Anstey, K. J., Parslow, R. A., Wen, W., Maller, J., Kumar, R., Christensen, H., & Jorm, A. F. (2006). Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. *Dementia and Geriatric Cognitive Disorders*, *21*, 300–308. https://doi.org/10.1159/000091438

Sadiq, F., Kronzer, V. L., Wildes, T. S., McKinnon, S. L., Sharma, A., Helsten, D. L., Scheier, L. M., Avidan, M. S., & Abdallah, A. B. (2018). Frailty phenotypes and relations with surgical

outcomes. *Anesthesia & Analgesia*, *127*(4), 1017–1027. https://doi.org/10.1213/ANE.0000000000003695

Sarksian, C. A., Gruenewald, T. L., Boscardin, J., & Seeman, T. E. (2008). Preliminary evidence for subdimensions of geriatric frailty: The MacArthur Study of Successful Aging. *Journal of the American Geriatrics Society*, *56*(12), 2292–2297. https://doi.org/doi:10.1111/j.1532-5415.2008.02041.x

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics*, *8*(24), 1–10. https://doi.org/10.1186/1471-2318-8-24

Searle, S. D., & Rockwood, K. (2015). Frailty and the risk of cognitive impairment. *Alzheimer's Research & Therapy*, *7*(54), 1–6. https://doi.org/10.1186/s13195-015-0140-3

Segaux, L., Oubaya, N., Broussier, A., Baude, M., Canouï-Poitrine, F., Naga, H., Laurent, M., Leissing-Desprez, C., Audureau, E., Ferrat, E., Chailloleau, C., Fromentin, I., David, J. P., & Bastuji-Garin, S. (2019). Identification of five frailty profiles in community-dwelling individuals aged 50–75: A latent class analysis of the SUCCEED survey data. *Maturitas*, *127*, 1–11. https://doi.org/10.1016/j.maturitas.2019.05.007

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., Kwak, Y., & Lipps, D. B. (2010). Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neuroscience and Biobehavioral Reviews*, *34*(5), 721–733. https://doi.org/10.1016/j.neubiorev.2009.10.005

Song, X., Mitnitski, A., & Rockwood, K. (2014). Age-related deficit accumulation and the risk of late-life dementia. *Alzheimer's Research & Therapy*, *6*(54), 1–13. https://doi.org/http://alzres.com/content/6/5/54

Sourial, N., Bergman, H., Karunananthan, S., Wolfson, C., Guralnik, J., Payette, H., Gutierrez-Robledo, L., Deeg, D. J. H., Fletcher, J. D., Puts, M. T. E., Zhu, B., & Béland, F. (2012). Contribution of frailty markers in explaining differences among individuals in five samples of older persons. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *67*(11), 1197–1204. https://doi.org/10.1093/gerona/gls084

Sugimoto, K., Rakugi, H., Kojima, T., Ishii, S., Akishita, M., Tamura, Y., Araki, A., Kozaki, K., Senda, K., Fukuoka, H., Satake, S., & Arai, H. (2020). Chapter 4 Frailty and specific diseases. *Geriatrics and Gerontology International*, *20*(S1), 25–37. https://doi.org/10.1111/ggi.13833

Thibeau, S., McDermott, K., McFall, G. P., Rockwood, K., & Dixon, R. A. (2019). Frailty effects on non-demented cognitive trajectories are moderated by sex and Alzheimer's genetic risk. *Alzheimer's Research & Therapy*, *11*(55), 1–15. https://doi.org/https://doi.org/10.1186/s13195-019-0509-9

Tierney, M. C., Curtis, A. F., Chertkow, H., & Rylett, R. J. (2017). Integrating sex and gender into neurodegeneration research: A six-component strategy. *Alzheimer's & Dementia: Translational Research and Clinical Interventions*, *3*, 660–667. https://doi.org/10.1016/j.trci.2017.10.006

Trevisan, C., Rizzuto, D., Maggi, S., Sergi, G., Welmer, A.-K., & Vetrano, D. L. (2019). Cross-sectional and longitudinal associations between peak expiratory flow and frailty in older adults. *Journal of Clinical Medicine*, *8*(1901), 1–12. https://doi.org/10.3390/jcm8111901

Vaz Fragoso, C. A., Enright, P. L., McAvay, G., Van Ness, P. H., & Gill, T. M. (2012). Frailty and respiratory impairment in older persons. *American Journal of Medicine*, *125*(1), 79–86. https://doi.org/10.1016/j.amjmed.2011.06.024

Vermunt, J. K. (2010). Latent class modeling with covariates: Two improved three-step approaches. *Political Analysis*, *18*, 450–469. https://doi.org/10.1093/pan/mpq025

Walston, J., Hadley, E. C., Ferrucci, L., Guralnik, J. M., Newman, A. B., Studenski, S. A., Ershler, W. B., Harris, T., & Fried, L. P. (2006). Research agenda for frailty in older adults: Toward a better understanding of physiology and etiology: Summary from the American Geriatrics Society/National Institute on Aging research conference on frailty in older adults. *Journal of the American Geriatrics Society*, *54*, 991–1001. https://doi.org/10.1111/j.1532-5415.2006.00745.x

Wolf, D. S., Gearing, M., Snowdon, D. A., Mori, H., Markesbery, W. R., & Mirra, S. S. (1999). Progression of regional neuropathology in Alzheimer disease and normal elderly: findings from the Nun study. *Alzheimer Disease and Associated Disorders*, *13*(4), 226–231. https://doi.org/10.1097/00002093-199910000-00009

Wu, Y. H., Liu, L. K., Chen, W. T., Lee, W. J., Peng, L. N., Wang, P. N., & Chen, L. K. (2015). Cognitive function in individuals with physical frailty but without dementia or cognitive complaints: results from the I-Lan Longitudinal Aging Study. *Journal of American Medical Directors Association*, *16*, 899.e9-899.e16. https://doi.org/10.1016/j.jamda.2015.07.013

Table 2-1. *Participant Characteristics at Baseline*

Characteristic	Total sample	Not-clinically-frail	Mobility-type	Respiratory-type	Sig.
Class prevalence n(%)	--	542 (84%)	59 (9%)	48 (7%)	
n(%) female	431 (66%)	351 (65%)	44 (75%)	36 (75%)	*ns*
Age (in years)	70.61 (8.64)	69.78 (8.39) [e]	78.21 (7.53) [f]	70.60 (8.27) [e]	***
Education (in years)	15.27 (2.97)	15.39 (2.94)	14.67 (2.83)	14.54 (3.34)	*ns*
APOE ε4+	150	132 (24%)	6 (11%)	12 (25%)	*ns*
Frailty index [a]	0.13 (0.07)	0.11 (0.06) [e]	0.22 (0.07) [f]	0.20 (0.07) [f]	***
MMSE	28.67 (1.25)	28.70 (1.24)	28.29 (1.39)	28.78 (1.11)	*ns*
Timed walk [b, c]	6.42 (1.65)	6.12 (1.13) [e]	9.28 (2.80) [f]	6.51 (1.65) [e]	***
Peak flow (L/min) [b, d]	421.98 (117.77)	435.40 (114.01) [e]	360.17 (100.86) [f]	329.10 (123.31) [g]	***

Note. Results presented as mean (standard deviation). *P* values are based on one-way ANOVA or chi-square tests, as appropriate. We adjusted for multiple comparisons using post-hoc Tukey tests. Values with different superscripts differ from one another. [a] We calculated the proportion of deficits for each person on the 50-item frailty index as reported in Thibeau et al. (2019). [b] We tested whether mobility- and respiratory-type differed from one another and the not-clinically-frail profile using planned comparisons. [c] The number of seconds taken to walk 20 feet. [d] The largest volume of air expired over three attempts.

*** $p < .001$

Table 2-2. *Multi-morbidity Items by Exploratory Factor Analysis Derived Frailty Domain*

Domain	Indictor
Mobility	Finger dexterity [a]
	Timed turn [a]
	Grip strength [b]
	Use of walker, cane, or wheelchair [c]
Instrumental health	Health has affected ability to travel [d]
	Health has affected ability to socialize [d]
	Health has affected ability to do hobbies [d]
	Health has affected ability to do mental activities [d]
	Health has affected ability to get around town [d]
	Health has affected ability to do chores [d]
Emotional wellbeing	Bradburn negative affect (restless, lonely, bored, depressed, upset due to criticism) [e]
	CES-D "during the past week, my sleep was restless" [f]
	CES-D "during the past week, I felt depressed" [f]
	CES-D "during the past week, I felt lonely" [f]
Comorbidity	Anemia [g]
	Sex-related health problems (i.e., gynecological problems or prostate problems) [g]
	Gastrointestinal problems (colitis/diverticulitis, gall bladder trouble, and/or liver trouble) [g]
	Kidney or bladder trouble [g]
Respiratory symptoms	Feeling short of breath [c]
	Bronchitis or emphysema [g]
	Asthma [g]
Cardiac symptoms	Pulse pressure [h]
	Heart trouble [g]
	Hardening of arteries (i.e., atherosclerosis) [g]

	High blood pressure [g]
	Stroke [g]
Physical activity	Stay at home but in chair most of the time [c]
	Health has affected ability to do physical recreational activities [d]
	Spinal condition and/or back trouble [g]
	Arthritis (rheumatoid and/or osteo) [g]

Note. [a] Performance was recoded as 0 (< 90th percentile) or 1 (within 90th percentile). [b] Performance was recoded as 0 or 1. See Supplementary Table 1, Appendix A. [c] 0 = no, 1 = yes. [d] 0 = no change, improved, N/A; 0.25 = slightly reduced; 0.50 = moderately reduced; 0.75 = drastically reduced; 1 = gave up doing activity. [e] 0 = no to all; 0.2 = yes to one; 0.4 = yes to two; 0.6 = yes to three; 0.8 = yes to four; 1 = yes to all. [f] 0 = rarely or none of the time; 0.33 = some or a little of the time; 0.67 = occasionally or a moderate amount of the time; 1 = most or all of the time. [g] 0 = no; 0.33 = yes, not serious; 0.67 = yes, moderately serious; 1 = yes, very serious. [h] Performance was recoded as 0 = 32.13–63.90; 0.5 = 64-75.9; 1 = 76+.

Table 2-3. *Model Fit Indices for One- to Four-Latent Profile Solutions*

Profile	(-)2LL	npar	AIC	BIC	SABIC	LMR	VLMR	Entropy
1	-5029.43	42	-4945.43	-4757.47	-4890.81	--	--	--
2	-5584.96	51	-5482.96	-5254.72	-5416.64	<.001	<.001	0.99
3	**-5880.55**	**60**	**-5760.55**	**-5492.02**	**-5682.52**	**<.001**	**<.001**	**0.99**
4 [b]	-6235.52	69	--	--	--	--	--	--

Note. (-2)LL, -2 log-likelihood; npar, number of parameters free; AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample size adjusted BIC; LMR, adjusted Lo-Mendell-Rubin likelihood ratio test; VLMR, adjusted Vuong-Lo-Mendell-Rubin likelihood ratio test. [b] This model was not considered due to non-replicated log-likelihood.

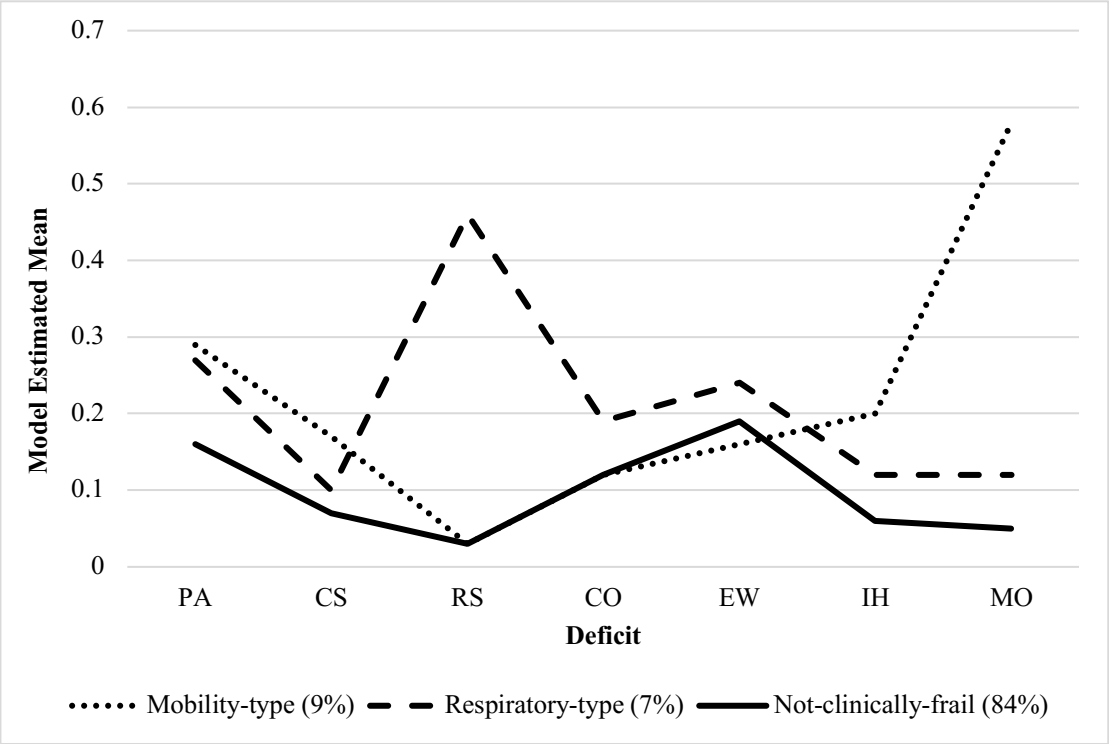


Figure 2-1. Model estimated observed indicator means for each latent profile. PA = Physical activity; CS = Cardiac symptoms; RS = Respiratory symptoms; CO = Comorbidity; EW = Emotional well-being; IH = Instrumental health; MO = Mobility. For further explanation of the profile interpretations see the Results section.

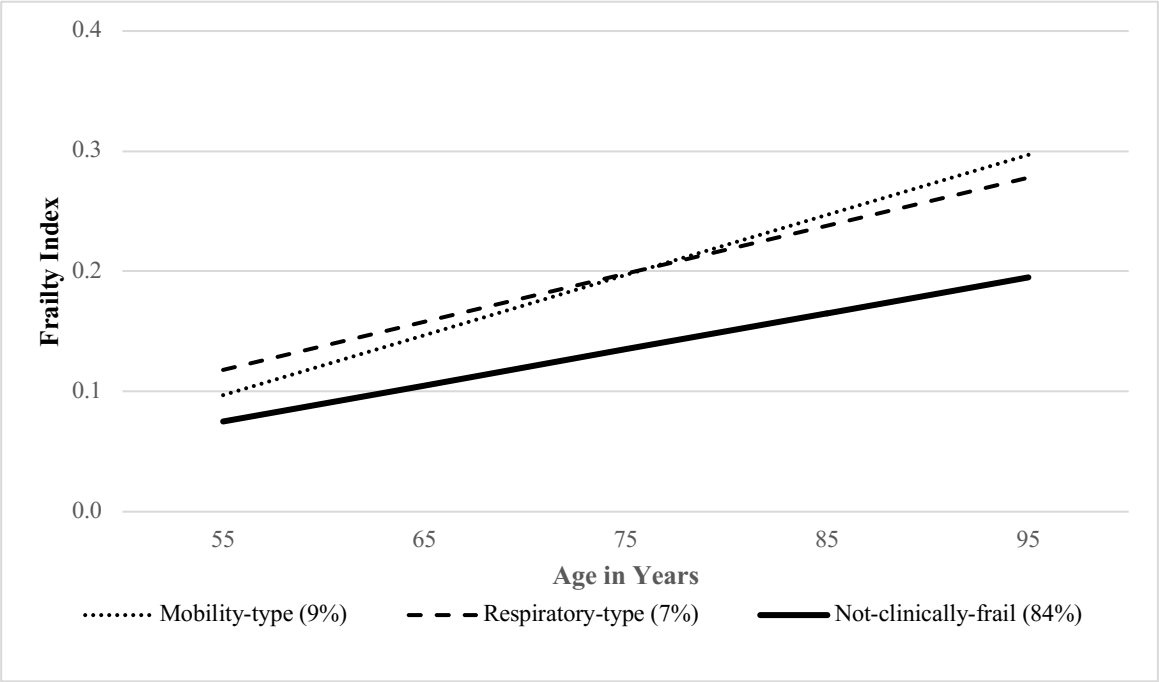


Figure 2-2. Predicted growth curve model for the 50-item frailty index across profile. Age in years was used as the metric of change and centered at 75 years. Profiles differed significantly in intercept and slope.

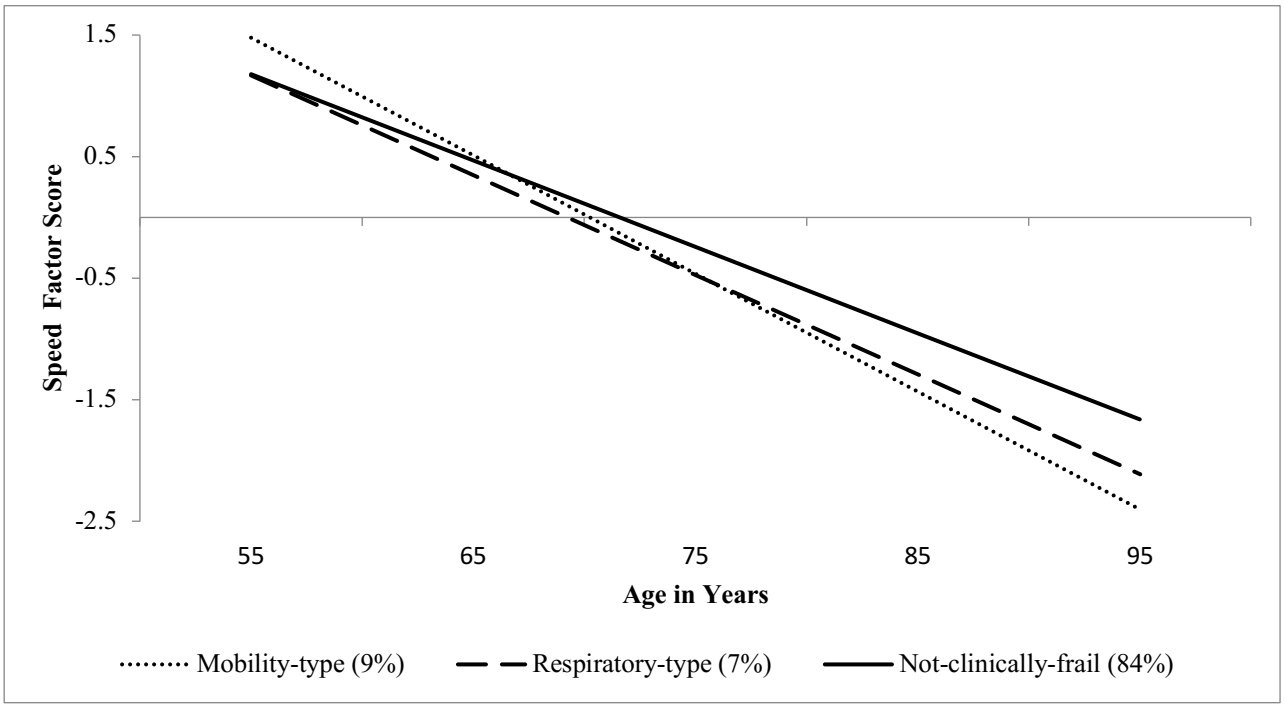


Figure 2-3. Predicted growth curve model for speed factor scores across profile. Age in years was used as the metric of change and centered at 75 years. Intercept was comparable across profiles. Slope differed significantly across profiles.

Chapter 3: Study 2

Tracking and Predicting Heterogenous Frailty Changes in Amnestic Mild Cognitive Impairment and Alzheimer's Disease: A Latent Transition Analysis

Background

Emerging literature suggests that frailty is a dynamic process, characterized by multidirectional trajectories of deficit accumulation (Fallah et al., 2011; Rogers et al., 2017; Thompson et al., 2018) or recurrent transitions between frailty states over time (Etman et al., 2012; Trevisan et al., 2017). A recent systematic review and meta-analysis assembled data from 16 studies for 42,775 community-dwelling older adults and examined transitions across physical frailty phenotypes over time (Kojima et al., 2019), including robust (0 deficits), pre-frail (1-2 deficits), and frail (3 or more of the following deficits: weight loss, exhaustion, weakness, slowness walking speed, and low physical activity; Fried et al., 2001). Results indicated that 13.7% of participants improved, 29.1% worsened, and 56.5% remained stable. The high degree of heterogeneity in frailty transition patterns persisted in sex stratification analyses. These results suggest that frailty can change in multiple directions, including the possibility of reversion from more to less frailty. It is important to note, however, that systematic investigations of heterogeneity in frailty progression remain relatively limited, and several reviews have issued a call for increased longitudinal epidemiological research on this topic (O'Caoimh et al., 2018; Rohrmann, 2020; Welstead et al., 2020). The present study fills in this gap by applying latent transition analysis (LTA) to a large database of longitudinal multi-morbidity indicators in order to (a) detect underlying clusters of aging multi-morbidity (or frailty statuses) across two measurement occasions and (b) examine patterns and predictors of frailty transitions.

LTA is a longitudinal extension of latent profile and latent class analysis— person-centered statistical approaches that can identify homogenous subgroups of individuals based on a set of observed indicators (Nylund-Gibson & Choi, 2018). Both are data-driven and person-centered analytic approaches. However, LTA includes two important features relevant to this study: (a) it

allows participants' profile memberships to change over time and (b) it provides the analytic tools to track and model these changes (Lanza & Collins, 2008). In the LTA approach, it is customary to use the term latent *statuses* (vs. profiles) to refer to the detected subgroups. This terminology better highlights the notion that subgroup membership is not fixed over time. We selected the LTA approach based on literature suggesting that alternate approaches to modeling change trajectories (e.g., latent growth curve analysis) may be less suitable for addressing research questions pertaining to multidimensional constructs, such as frailty (Clegg et al., 2013), which may evince multidirectional patterns of transitions over time (Lanza & Collins, 2008).

To our knowledge, only one study has modeled heterogeneity in frailty emergence and progression using LTA. In this study, Lafortune and colleagues (2009) applied LTA to 17 multi-morbidity indictors collected from a baseline sample of 1,164 cognitively normal community-dwelling frail older adults (age range: 64–104 years; 71% female). Participants were followed over three measurement occasions (12- and 22-month follow-up) and contributed longitudinal data related to chronic health conditions, cognitive deficits, depression, sensory limitations, functional limitations, and impairment in activities of daily living. Results showed that (a) a four-status solution provided the best fit to the data at each measurement occasion and (b) latent statuses were invariant over time (i.e., retained the same substantive interpretation across measurement occasions). Statuses were distinguished primarily on the basis of the pattern and severity of deficits observed in the physical and cognitive domain and subsequently interpreted as: (a) *cognitively and physically impaired*, (b) *cognitively impaired*, (c) *physically impaired*, and (d) *relatively healthy*. Transition analyses showed that older adults classified as *cognitively and physically impaired* or *cognitively impaired* had a higher probability of unfavorable transitions, lower probability of improvement, and increased mortality risk. Interestingly, frailty transition patterns and mortality

risk were also reported to vary as a function of sex. These results suggest that, within this 17-item roster of morbidities, cognitive deficits portended a poorer prognosis for frailty emergence and progression. Although a promising approach with novel results, this study was limited by (a) the relatively small number and limited breadth of the morbidity indicators and (b) reporting of pertinent clinical characteristics of the study sample. For example, with respect to the former, cognitive deficits were indexed by scores on the Short Portable Mental Health Questionnaire (Pfeiffer, 1975)— a brief cognitive screening instrument that may be limited in diagnostic and clinical utility due to its low sensitivity and specificity (Malhotra et al., 2013). With respect to the latter, the authors noted that all study participants were frail but provided no summary measure of frailty levels at baseline or follow-up.

The current research builds on this limited prior work by assembling longitudinal data from the National Alzheimer's Coordinating Center (NACC) for two related clinical cohorts of older adults. Specifically, we included persons with a baseline diagnosis of amnestic mild cognitive impairment (aMCI; baseline n = 878) or Alzheimer's disease (AD; baseline n = 2,196). We subsequently applied LTA to data for the entire study sample in order to examine two specific research aims: (a) detect underlying clusters of aging multi-morbidity across two measurement occasions and (b) examine patterns of frailty emergence and progression in relation to the two clinical cohorts. Regarding the latter, we tested baseline clinical cohort as a predictor of (a) baseline membership in the detected statuses and (b) the probability of transitioning across latent frailty statuses. We note that two data-driven analytic approaches would have been possible. We selected a full clinical cohort approach over a multiple-group (aMCI, AD) approach because a substantial subset of participants changed diagnosis across the study duration. In a typical multiple-group LTA, the grouping variable does not vary across the study duration (Collins & Lanza, 2010).

However, in the present study, between Time 1 and Time 2, 64 (7.3%) participants with aMCI transitioned to cognitively normal and 366 (41.7%) participants transitioned to AD. This pattern is consistent with literature characterizing aMCI as a transitional (and potentially reversible) stage between normal cognitive aging and dementia (Fischer et al., 2007; Janoutová et al., 2015).

We elected to exclude participants who were cognitively normal at baseline for two reasons. First, preliminary analyses indicated that cognitively normal participants in the NACC reported relatively low levels of frailty, and as such, we were unable to detect significant heterogeneity in frailty subtype emergence and progression. Second, previous studies that assembled multi-morbidity data for a range of clinical cohorts and subsequently considered cognitive status as amongst one of the indicators of aging morbidity were unable to detect significant heterogeneity within cognitively impaired samples (Ng et al., 2019; Whitson et al., 2016). That is, participants with cognitive impairment or dementia tended to be classified into a single data-driven subtype. For example, Whitson et al. (2016) applied latent class analysis to 13 multi-morbidity indicators and identified six classes that were distinguished by which conditions had excess prevalence, including *minimal disease*, *nonvascular*, *vascular*, *cardio-stroke-cancer,* and *very sick*. Importantly, they also detected a *major neurological disease* class, which was characterized by an excess prevalence of AD, Parkinson's disease, and related psychiatric disorders. The current study was designed to avoid detecting such a pattern in our data.

Interestingly, two recent studies assembled multi-morbidity data from the NACC, and each calculated a 45-item frailty index in order to examine how the risk for MCI and/or dementia varies according to the proportion of deficits accumulated at baseline (Ward et al., 2021a, 2021b). Results from the first study revealed that, amongst participants who were classified as cognitively normal at baseline, a higher degree of frailty predicted an increased risk for MCI (amnestic or non-

amnestic; single-or multi-domain) or all-cause dementia at a 12-month follow-up (Ward et al., 2021a). Amongst those who were classified as having MCI at baseline, a higher degree of frailty predicted an increased risk for dementia conversion and a lower probability of being reclassified as cognitively normal. In the second study, Ward and colleagues (2021b) examined whether frailty was differentially related to the risk for all-cause dementia amongst participants with a baseline diagnosis of aMCI as compared to non-aMCI (single- or multi-domain). Results indicated that, over a follow-up period ranging between 6 months to 14 years (median = 4.10 years), frailty predicted an increased risk for dementia development across both subtypes. However, this association was comparatively stronger for non-aMCI.

A small number of cross-sectional studies have applied person-centered analytical approaches (e.g., cluster analysis or latent class analysis) to a database of multi-morbidity indicators in order to detect frailty subtypes across a range of normal cognitive aging, impairment, dementia (Bandelow et al., 2016; Looman et al., 2018; Majnarić et al., 2020) and the findings reported converge with earlier research (Lafortune et al., 2009). For example, Looman and colleagues distinguished the following six profiles that were ordered based on the pattern and severity of deficits accumulated at baseline: (a) *relatively healthy*, characterized by limited problems across domains; (b) *mild physically frail*, characterized by minor problems in the physical domain; (c) *psychologically frail*, characterized by physical impairments and mental health concerns; (d) *severe physically frail*, characterized by pronounced physical impairments; (e) *medically frail*, characterized by impairments in the physical, psychological, and social domain; and (f) *multi-frail,* characterized by severe deficits in the physical, psychological, functional, social, and cognitive domains. Importantly, dementia (0 = no self-reported history; 1 = self-reported history) was included as amongst one of the indicators of aging morbidity considered in

this study. Post-hoc analyses revealed that participants classified as *multi-frail* had the highest dementia prevalence as well as the highest values on an independently calculated 45-item frailty index. More recent research reported that older adults with MCI had a greater likelihood of being classified into profiles characterized by a higher level of physical frailty as compared to cognitively normal older adults (Majnarić et al., 2020).

The foregoing results suggest that cognitive impairment and frailty may co-exist and mutually interact (Godin et al., 2017). Nevertheless, to our knowledge, no studies have examined the association between cognitive status (or function) and frailty subtype emergence or progression. This is a priority area of research attention. A recent systematic review issued a call for future studies to examine patterns and predictors of frailty transitions amongst less-represented populations (Welstead et al., 2020), including cognitively impaired samples. Findings from this line of research have applications for precision interventions to better identify and treat older adults with aMCI or AD who may be at risk for adverse frailty transitions. Early and targeted interventions may not only reduce the risk for conversion from MCI to AD (Ward et al., 2021b), but also attenuate the rate of cognitive decline amongst older adults living with these clinical conditions (Buchman et al., 2007; Robertson et al., 2013).

Importantly, following from the recommendations outlined in Welstead et al. (2020), we also tested non-modifiable (i.e., sex, Apolipoprotein E [*APOE*] ε4 allele carrier status, race/ethnicity, and chronological age) and potentially modifiable (i.e., global cognition, clinical cohort, and education) baseline risk characteristics as predictors of baseline membership and frailty transition patterns. Sex differences in frailty transitions are a topic of increased research interest (Chong et al., 2015; Etman et al., 2012; Hubbard, 2015; Kojima et al., 2019; Thompson et al., 2018; Welstead et al., 2020). A recent systematic review concluded that females consistently have higher levels of

frailty relative to same age males and yet they are better able to tolerate these deficits, as evidenced by their lower mortality rates at any given level of frailty (Gordon et al., 2017). Several biological, social, and behavioral mechanisms are posited to underlie this sex-frailty paradox (Hubbard, 2015; Hubbard & Rockwood, 2011). However, this pattern remains a fundamental paradox of aging (Blagosklonny, 2007). A small number of studies have examined whether the greater longevity of females may also be attributed to sex differences in the patterns and/or progression of multi-domain deficit accumulation (Garre-Olmo et al., 2013; Lafortune et al., 2009; Zhang et al., 2020), but the results are inconsistent. Similarly, findings from the limited literature examining *APOE*-frailty associations are equivocal. For example, one study found no evidence in support of *APOE*-frailty associations (Rockwood et al., 2008), whereas more recent research reported that carriers of the ε4 risk allele were selectively sensitive to frailty effects on exacerbated memory decline (Thibeau et al., 2019). To our knowledge, no prior works have tested whether data-driven frailty subtype emergence and progression varies as a function of *APOE* ε4 carrier status.

Notably, findings from related research examining racial/ethnic differences in aging multi-morbidity suggest that this is a promising area of research attention (Liu et al., 2014). For example, Liang et al. (2009) identified three clusters of functional decline using person-centered analytical techniques (i.e., group-based semiparametric mixture models), including *healthy functioning*, *moderate functional decrement*, and *large functional decrement*. The authors reported that, relative to non-Hispanic Whites, Black/African American or Hispanic participants were more likely to be classified into the latter two clusters as compared to *healthy functioning.* Accordingly, in the present study we tested whether baseline status membership and progression varied for non-Hispanic Whites as compared to Black/African Americans. Consistent with the approach undertaken in previous frailty-related research (Lafortune et al., 2009) and the prevailing literature

on potentially modifiable risk factors for adverse frailty trajectories (Welstead et al., 2020), we also tested chronological age, global cognition, and education as potential predictors of these outcomes.

Research Goals

The specific research goals (RG) of this study were as follows. For RG1, we applied LTA to data for the entire study sample in order to detect underlying statuses of aging multi-morbidity and to characterize patterns of frailty transitions. Our expectations for these results were two-fold. First, we anticipated that results from these analyses would reveal data-driven frailty statuses that were differentiated by the pattern and severity of deficits accumulated at baseline and follow-up (Lafortune et al., 2009). Second, we expected that results from the LTA would reveal significant heterogeneity in frailty progression such that subsets of participants would transition towards statuses representing a higher burden of frailty, others would show stability in frailty progression, and the remaining participants would transition towards statuses representing a lower frailty burden. For RG2, we sought to identify significant predictors of (a) baseline membership in the detected latent status and (b) frailty transition patterns. We predicted that clinical cohort (AD), *APOE* (ε4 carriers), race/ethnicity (Black/African American), chronological age (older), global cognition (poorer performance), and education (less years) would portend a worse prognosis for baseline status membership and progression. Whether our results would generalize (Bohn et al., 2021) or vary (Hubbard & Rockwood, 2011) across sex was an empirical question.

Methods

NACC Dataset

Data for this study were drawn from the Uniform Data Set (UDS) of the NACC. The UDS was implemented in 2005 by the National Institute on Aging Alzheimer Disease Centers (ADCs) program (Weintraub et al., 2018). To date, 39 ADCs across the United States have contributed

harmonized, large-scale, longitudinal data to the UDS with the overarching goal of advancing collaborative research on early detection, diagnosis, treatment, and prevention of age-related neurodegenerative disease. Clinical cohorts of older adults are recruited— primarily through convenience sampling methods— to the UDS and followed approximately annually. Cognitive status is determined by ADC clinicians based on prevailing diagnostic research criteria (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). Participants determined to have MCI or all-cause dementia are subsequently evaluated for primary and contributing etiologic diagnoses (Besser et al., 2018). At each measurement occasion, participants are administered a comprehensive testing battery spanning demographic, clinical, neurological, neuropsychological, health, lifestyle, and functional domains (Beekly et al., 2007). Informed consent is provided at the individual ADCs, as approved by individual Institutional Review Boards (IRB). The University of Washington's IRB approved the sharing of deidentified data from the UDS (Weintraub et al., 2018).

Participants

We assembled data for all UDS visits conducted between January 2005 to March 2020. We selected for inclusion all three versions of the UDS testing battery (see Besser et al. (2018) for an overview of revisions undertaken between UDS Versions 1.0–3.0). As displayed in Figure 3-1, we developed firm rules of inclusion and exclusion and applied them to the full UDS (n = 42,661) in a series of data selection steps. We briefly summarize here the selection criteria we applied in assembling the dataset. We began by stipulating five fundamental requirements for our research sample, including: (a) timepoints (restricted to participants with a minimum of three waves); (b) follow-up (restricted to in-person visits); (c) inter-wave intervals (restricted to intervals within +/- 1 SD from the mean); (d) age (restricted to ≥ 53 years at baseline); and (e) clinical cohort (restricted

to participants classified at baseline as having MCI or dementia). We then disaggregated the sample by clinical cohort and applied the following exclusionary criteria across three measurement occasions: (a) cognitive impairment (restricted to single- or multi-domain aMCI) and (b) primary etiologic diagnosis (restricted to AD).

We applied the following exclusionary criteria at baseline: (a) dementia severity (restricted to mild or moderate); (b) living situation (restricted to private residence or retirement community); (c) psychiatric disorders (restricted to participants without obsessive compulsive disorder, bipolar disorder, or schizophrenia); (d) traumatic brain injury (restricted to participants without a self-reported history); and (e) race/ethnicity (restricted to non-Hispanic White or Black/African American). In Table 3-1, we present baseline descriptive and clinical characteristics for the final study sample (N = 3,074; 52% female; Mage = 74.70; range = 53 – 100 years; 91% non-Hispanic White).

Measures

Multi-morbidity data. We identified 59 candidate multi-morbidity items (see Table 3-2) using three waves of data from the UDS. Data for these items were collected using self-report, clinician examinations, and formal tests with standardized scales. Items were recoded such that values ranged from 0 (no deficit present) to 1 (deficit was maximally expressed; Searle et al., 2008). Prospective items were selected based on the following considerations. First, many of these indicators are harmonized with Study 1 of the dissertation research (Chapter 2; Bohn et al., 2021). For example, we assembled indicators related to mobility function, instrumental health, emotional well-being, comorbidities, cardiovascular symptoms, and physical activity. Due to unavailability in this dataset, we were unable to assemble indicators related to respiratory symptoms and diseases. Importantly, however, we assembled indicators related to systems of aging morbidity that were not

previously considered due to unavailability (e.g., nutritional status and deficiencies). Second, these items harmonize with those used in previous frailty-related research conducted (a) using data from the UDS (Ward et al., 2021a, 2021b) and (b) with cognitively impaired samples (Burt et al., 2019; Looman et al., 2018; Mitnitski et al., 2001; Rockwood et al., 2016; Wallace et al., 2019).

Candidate multi-morbidity items were screened for eligibility using standard criteria (Searle et al., 2008). We subsequently removed 16 items that were deemed to be redundant, did not accumulate with age, or saturated too early. Data for the final set of 43 multi-morbidity items (see Table 3-3) were (a) submitted to an exploratory factor analysis (EFA; consistent with the approach undertaken in Bohn et al., 2021) and (b) separately used to calculate a cumulative 43-item frailty index. Values on the frailty index represent the proportion of deficits accumulated and can range between 0 (no deficits endorsed) and 1 (all deficits endorsed). Baseline descriptive statistics for the frailty index are presented in Table 3-1.

Importantly, results from preliminary data-checking analyses conducted with the final set of multi-morbidity indicators revealed that there was limited change across many of the items from the first to second measurement occasion. We reasoned that this may be due in part to the relatively close spacing of the study intervals (*M* interval = 394.44 days; *SD* = 58.40), and as such, opted to perform our analyses using data from the first and third measurement occasion (hereafter referred to as Time 1 and 2, respectively; *M* interval = 780.01 days; *SD* = 78.88).

Time 1 predictors. We assembled baseline data for clinical cohort (0 = aMCI; 1 = AD) and self-reported measures of sex (0 = male; 1 = female), race/ethnicity (0 = non-Hispanic White; 1 = Black/African American), chronological age (in years), and educational background (total number of years). Depending on the version of the neuropsychological testing battery completed at baseline, participants were administered either the Mini Mental State Examination (MMSE;

Folstein & Folstein, 1975) or the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) as a measure of global cognitive function. Participants completing the MoCA were assigned an equivalent score on the MMSE using published NACC conversion tables (Monsell et al., 2016). A subset of the study participants (n = 2,719) submitted blood samples to the NACC for genotyping. For these individuals, we assembled data pertaining to *APOE* ε4 allelic status (non-carrier = 0; carrier = 1). Because previous research indicates that the ε2 allele represents a protection factor and the ε4 allele represents a risk factor (McFall et al., 2015), participants with the ε2/ε4 genotype (n = 70) were excluded from the corresponding prediction analyses. We present descriptive statistics for baseline risk characteristics in Table 3-1.

Analytical Approach

Analyses were conducted using Mplus 8.0 (Muthén & Muthén, 1998-2017). Missing data for the multi-morbidity items were assumed to be missing completely at random (i.e., item nonresponse; Little, 2013) and were handled using full-information maximum likelihood. This approach estimates model parameters and standard errors directly from the available data (Enders, 2011; Little, 2013). A small number of participants were missing baseline data for global cognitive function (n = 75; 2.4%) or educational background (n = 7; 0.2%). We estimated these missing data using multiple imputations. This approach involves the following three steps: (a) plausible replacement values for missing predictor variables are imputed; (b) the analysis is conducted using multiple versions or replications of the imputed dataset; and (c) model parameters and standard errors are estimated by pooling results across the imputed datasets (Enders, 2011). In accordance with prevailing conventions (Enders, 2011; Little, 2013) and previous VLS research (Bohn et al., 2020), we generated 20 imputations of the dataset and pooled these for all prediction analyses.

Exploratory and confirmatory factor analysis. Time 1 multi-morbidity data were submitted to an EFA in order to (a) reduce the total number of items for estimation feasibility in the LTA and (b) identify salient domains of aging morbidity. We performed these analyses using data for a random subset (i.e., 50%) of the overall study sample. Decisions regarding the number of factors (or frailty-related domains) and indicators to retain were made in accordance with best-practices literature (Costello & Osborne, 2005; Muthén & Muthén, 2009). We verified that this latent structure fit the data at Time 1 and Time 2 (separately) by applying confirmatory factor analysis (CFA) to (a) data for the remaining subset of participants not used in the EFA and (b) data for the entire study sample. Model fit was determined using the following standard indices: (a) chi-square, for which a good fit would produce a non-significant result (i.e., $p > .05$; indicates that the data do not significantly differ from model-based estimates); (b) the comparative fit index, for which fit is judged by a value of $\geq .95$ as good and $\geq .90$ as adequate; (c) root mean square error of approximation, for which fit is judged by a value of $\leq .05$ as good and $\leq .08$ as adequate, and (d) Tucker-Lewis Index, for which fit is judged by a value of $\geq .95$ as good and $\geq .90$ as adequate (Little, 2013). The resulting factors (or domains of aging morbidity) were interpreted using previous research. The proportion of deficits accumulated in each domain, at each time point, was subsequently calculated for each participant and used as continuous observed indicators in the LTA. Values could range between 0 and 1, with higher values denoting greater impairment.

Latent transition analysis. The LTA was conducted in four sequential phases. In the first phase, we performed a separate LPA at each time point (Connell et al., 2008). This entailed fitting a sequence of models with varying numbers of latent statuses (e.g., 1, 2, 3). As before (Bohn et al., 2021), we determined the optimal number of latent statuses by considering interpretability of the model results, together with the following model parameters, tests, and fit indices (Masyn, 2012):

(a) log-likelihood value (*LL*); (b) number of parameters estimated; (c) Bayesian Information Criterion (BIC); (d) sample-size adjusted BIC (SABIC); (e) Akaike Information Criterion (AIC); (f) adjusted Lo-Mendell-Rubin likelihood ratio test (LMR-LRT); and (g) adjusted Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR-LRT). Lower values of BIC, SABIC, and AIC denote better fit. The LMR-LRT and VLMR-LRT test the current model (*k*) against the model with one less latent status (*k*-1) and are interpreted such that a non-significant *p*-value supports selecting the *k*-1 model (Nylund-Gibson & Choi, 2018). Entropy was not used for model selection, but rather to infer the accuracy with which participants were classified into the latent statuses (ranges between 0 – 1; higher values denote better classification accuracy). Consistent with Study 1 (Bohn et al., 2021), we used 5000 multiple starting values in order to avoid local maxima. Indicators were allowed to covary within status, while the variances-covariances were constrained to be equal across statuses (i.e., class invariant-unrestricted structure). Preliminary analyses indicated that this variance-covariance structure provided the best fit to the data (as compared to alternative models that allowed free estimation of variance-covariance structures across latent statuses).

In the second phase, we examined longitudinal measurement invariance of the latent statuses. This involves conducting the following sequence of similarity tests (Morin et al., 2016; Morin & Litalien, 2017): (a) configural similarity, which tests whether the same number of latent statuses based on the same indicators can be identified over time; (b) structural similarity, which tests whether within-status means are the same over time; (c) dispersion similarity, which tests whether within-status variances are the same over time; and (d) distributional similarity, which tests whether the relative size of the statuses is the same over time. Importantly, only structural invariance is required to proceed with subsequent steps in the LTA (Morin et al., 2016). Constraining model estimated means to be equal over time facilitates model identification by (a)

reducing the number of parameters that must be estimated and (b) ensures that the meaning or substantive interpretation of the latent statuses remains constant across the study duration (Collins & Lanza, 2010). We tested the tenability of invariance assumptions by comparing models with unconstrained and constrained parameters using -2 *LL* difference statistic (Collins & Lanza, 2010). The most similar unconditional LTA model was retained and interpreted.

As in Study 1 (Bohn et al., 2021), latent statuses were interpreted using an adapted formula for Cohen's *d*. This formula is used to (a) calculate standardized mean differences across latent statuses in the observed indicators and (b) facilitate assigning qualitative labels to the detected latent statuses. Standardized mean differences > 2.0 indicate a less than 20% overlap in status-specific distributions and a high degree of separation on the associated indicator, whereas values < 0.85 indicate more than 50% overlap and a low degree of separation on the associated indicator. Standardized mean differences > 1.5 are often used to interpret and subsequently assign qualitative labels to the detected latent statuses (Masyn, 2012).

In the third phase, we examined patterns of frailty transitions. To do this, we first assigned participants into their most likely latent status at each time point based on estimated posterior probabilities. This approach accords with previous developmental research (Bray et al., 2015; Nylund-Gibson et al., 2014; Seaton et al., 2012; Wong et al., 2012) and has the advantage of allowing researchers to treat latent status membership as an observed variable within a larger and more complex model of empirical interest (Bray et al., 2015; Clark & Muthén, 2009). This approach is suitable for use in mixture models that are characterized by high entropy (> .80) and large sample sizes (Asparouhov & Muthén, 2014; Clark & Muthén, 2009). We subsequently calculated a 2 x 4 matrix of transition probabilities from Time 1 to Time 2 (Lanza et al., 2010;

Lanza & Collins, 2008). These values reflect the probability of being in a given status at Time 2, conditional on being in a given status at Time 1.

In the fourth phase, we performed prediction analyses in two sequential stages. In stage one, we sought to identify significant predictors of Time 1 latent status membership using multinomial logistic regression. As noted above, only a subset of participants had data available for *APOE* ε4 allelic status. Rather than impute these data (published attempts to recover missing genes across an entire dataset remain limited; Bobak et al., 2020), we opted to perform two multinomial logistic regressions— one with the entire study sample (*APOE* excluded) and the other with the genotyped subsample (*APOE* included together with the remaining predictors). For the latter analysis, we report only the results for *APOE* (and not the remaining predictors). In the second step, we aimed to identify significant predictors of the probability of transitioning across latent statuses using multinomial logistic regression. Consistent with previous research (Nylund-Gibson et al., 2014), we performed this analysis by regressing Time 2 latent status on (a) Time 1 latent status (results not reported below), (b) baseline risk characteristics (results not reported below), and (c) interaction terms that allowed for the transition probabilities to vary as a function of the considered predictors (results reported below). That is, the interaction terms allowed us to test whether Time 1 predictors affected the probability of older adults transitioning across the data-driven frailty statuses. We performed these analyses first for the entire study sample (excluding *APOE*) and then for the genotyped subsample (*APOE* included together with the remaining predictors). For the latter analysis, we report only the results for *APOE*.

Results

Foundational analyses: Exploratory and confirmatory factor analysis

The EFA revealed five latent factors that accounted for associations amongst the 43 multi-morbidity indicators. Consistent with previous research (Bohn et al., 2021; Cummings, 1997; Kamaruzzaman et al., 2010; Lafortune et al., 2009; Montero-Odasso et al., 2009; Sadiq et al., 2018; Yesavage & Sheikh, 1986), we labeled these factors according to the items loading on them. Specifically, the observed domains of frailty included: (a) *ambulatory ability* (e.g., bowel incontinence; slowing of motor movements; total *n* indicators = 5), (b) *emotional wellbeing* (e.g., satisfied with life; often feel helpless; total *n* indicators = 5), (c) *behavioral disturbances* (e.g., disinhibition; nighttime behaviors; total *n* indicators = 9), (d) *instrumental health* (e.g., difficulty traveling in neighbourhood; difficulty shopping alone; total *n* indicators = 10), and (e) *cardiovascular symptoms* (e.g., hypercholesterolemia; diabetes; total *n* indicators = 4). We present the EFA derived domains together with the corresponding indicators in Table 3-4.

Results from the CFA conducted with (a) the subset of the data not used in the EFA and (b) the entire study sample showed adequate model fit at both time points (see Table 3-5 for model fit indices). We note that model fit at each time point could have been strengthened by correlating indicators with similar methodology (e.g., multi-morbidity indicators drawn from the same scale; Little, 2013). However, because we are not estimating factor scores at each time point but rather calculating the proportion of deficits accumulated using observed data, we report model fit indices for the most restrictive CFA model (i.e., the null model, which assumes that model indicators are not correlated). Importantly, all indicators had strong loadings on the corresponding latent construct. We display the CFA model applied to data for the entire study sample at both time points in Figures 3-2 and 3-3.

RG1: Latent transition analysis

Step 1: LPA conducted at each time point. We present results from the LPA conducted at each time point in Table 3-6. Findings indicated that AIC, BIC, and SABIC all steadily decreased as the number of latent profiles increased at Time 1, indicating that model fit improved with the addition of each latent profile. The adjusted LMR-LRT (p = .11) and VLMR-LRT (p = .11) suggested that the three-profile solution did not provide a better fit to the data relative to the two-profile solution. Further, participants in the latter solution were classified into the profiles with a high degree of precision (entropy = 0.99). We therefore selected the two-profile solution as the final model at this time point. Results for Time 2 indicated that AIC, BIC, and SABIC all steadily decreased with the addition of each successive latent profile. The adjusted LMR-LRT (p = 1.0) and VLMR-LRT (p = 1.0) indicated that the five-profile solution did not provide a better fit to the data relative to the four-profile solution. Because participants in the latter solution were also classified into the profiles with a high degree of precision (entropy = 0.91), we selected the four-profile solution as the final model at this time point.

Step 2: Longitudinal measurement invariance and status interpretations. Findings from the longitudinal measurement invariance tests are presented in Table 3-7. Because results from the LPA conducted at each time point indicated that a different number of latent profiles provided the best fit to the data, our findings did not support configural or distributional invariance (no formal tests were required). This pattern of results is often expected in developmental and aging research (Collins & Lanza, 2010). We subsequently tested for structural invariance by estimating two models. In the first model, within-status indicator means were free to vary across time. In the second model, indicator means of the two latent statuses detected at Time 1 were constrained to be equal to two of the latent statuses detected at Time 2. As highlighted in Table 3-7, these constraints significantly improved model fit. We subsequently tested for distributional invariance in a third

model. This model was identical to the second model, with the exception that within-status variances were also constrained to equality across time. Model fit significantly worsened with the addition of these constraints. As such, we selected the second model as the final unconditional LTA model.

Model estimated indicator means for the final solution are depicted in Figure 3-4. Standardized mean differences are presented in Table 3-8. These values collectively formed the basis for interpreting and labeling the frailty statuses. At Time 1, we interpreted the data-driven frailty statuses as *Not-Clinically Frail* (n = 2,790; 91%) and *Moderately Frail* (n = 284; 9%). At Time 2, we again detected the *Not-Clinically Frail* (n = 1,714; 56%) and *Moderately Frail* statuses (n = 571; 19%). However, we also identified two novel and complementary frailty statuses that we interpreted as *Mildly Frail* (n = 654; 21%) and *Severely Frail* (n = 153; 4%). The rationales behind the foregoing interpretations are as follows. At both time points, the Not-Clinically Frail status was characterized by comparatively lower levels of impairment across domains of aging morbidity. Although the standardized mean differences outlined in Table 3-8 do not all show a high degree of class separation, the general pattern is consistent with our interpretation that Not-Clinically Frail participants endorsed the lowest level of aging morbidity features. Further, participants classified into this status had lower baseline values on the independently calculated 43-item frailty index (M = 0.22; SD = 0.12) relative to Moderately Frail participants (M = 0.37; SD = 0.13; $t(3{,}035) = -19.17$, $p < .001$). This pattern persisted at Time 2, such that Not-Clinically Frail participants had the lowest frailty index values (M = 0.26; SD = 0.13; $F(3, 3{,}051) = 377.31$, $p < .001$). The Mildly and Moderately Frail statuses were largely ordered along a continuum representing an increasing proportion of deficits accumulated— particularly in terms of ambulatory ability— and successively higher values on the frailty index (M_{Mild} = 0.33; SD = 0.14; $M_{Moderate}$= 0.43; SD = 0.14). The

Severely Frail status was characterized by pronounced deficits in ambulatory ability and instrumental health, as well as the highest values on the frailty index (M = 0.55; SD = 0.14). In Table 3-9, we present baseline descriptive statistics disaggregated by latent status membership.

Step 3: Transition probabilities. Unconditional latent transition probabilities are presented in in Table 3-10. These values collectively represent patterns of change for all members in a given frailty status from the first to second measurement occasion (i.e., collapsing across the risk characteristics reported below for RG2). Findings indicated that older adults who were Not-Clinically Frail at Time 1 had a 0.61 probability of remaining in this status at Time 2. Put differently, 61% of the Not-Clinically Frail participants remained stable in their status membership over time. Of the Not-Clinically Frail participants who transitioned, the most common trajectory was towards the Mildly Frail status (0.21). Not-Clinically Frail participants were comparatively less likely to transition towards the Moderately Frail status (0.15) and very unlikely to progress towards the Severely Frail status (0.03). Conversely, the latter two transition patterns were amongst the most common for participants who were Moderately Frail. Specifically, results indicated that 55% and 21% of these participants remained Moderately Frail or progressed towards the Severely Frail status, respectively. Notably, a subset of Moderately Frail participants reverted to the Mildly Frail (0.17) or Not-Clinically Frail (0.07) status at Time 2. We tested and confirmed in a series of follow-up analyses (results not shown) that these transition probabilities differed significantly (a) across baseline frailty statuses and (b) within baseline frailty statuses.

RG2: Prediction of baseline membership and transition probabilities

Step 1: Predicting baseline status membership. We present odds ratios ([OR]; exponentiated logistic regression coefficients) from the multinomial logistic regression predicting baseline status membership in Table 3-11. These values represent the conditional effect of each predictor on the

likelihood of being classified into the Moderately Frail as compared to Not-Clinically Frail status. OR larger than 1.0 denote an increased risk for the former status, whereas OR less than 1.0 denote a reduced risk. Results indicated that older age (1.08) and a baseline diagnosis of AD (OR = 1.79) increased risk for being classified as Moderately Frail, while female sex (OR = 0.75) and better global cognitive function (OR = 0.97) predicted a reduced risk. Race/ethnicity, educational background, and *APOE* ε4 carrier status did not yield significant results.

Step 2: Predicting latent transition probabilities. Our results indicated that select transition probabilities varied as a function of race/ethnicity, age, and *APOE* carrier status. Significant interactions were probed by (a) stratifying the sample by Time 1 status (i.e., Not-Clinically Frail and Moderately Frail) and (b) examining the independent effect of race/ethnicity, age, and *APOE*. Importantly, results for race/ethnicity were no longer significant when we performed prediction analyses stratified by Time 1 status. That is, transition probabilities for Not-Clinically Frail and Moderately Frail participants did not vary as a function of racial/ethnic background. We attribute this finding to the relatively small proportion of participants who were Black/African American, which may have reduced power to detect significant differences. Specifically, 9% of the Not-Clinically Frail participants (n = 259) and 12% of the participants with Moderately Frail participants (n = 33) at Time 1 were Black/African American.

Results for chronological age and *APOE* remained significant in stratification analyses. With respect to the former, we found that older age predicted an increased likelihood of Not-Clinically Frail participants progressing towards the Mildly Frail status (OR = 1.05; 95% CI = 1.04, 1.06) as compared to remaining Not-Clinically Frail. Conversely, age was unrelated to the likelihood of Moderately Frail participants reverting to the Mildly Frail as compared to Not-Clinically Frail status (OR = 0.98; p = 0.46). With respect to *APOE*, we found that Not-Clinically Frail participants

who carried the risk allele were less likely to progress towards the Mildly Frail (OR = .0.81; 95% CI = 0.68, 0.96) or Moderately Frail statuses (OR = 0.62; 95% CI = 0.51, 0.75) as compared to remaining Not-Clinically Frail. In contrast, Moderately Frail participants who carried the risk allele were more likely to revert to the Mildly Frail status as compared to (a) transitioning to the Not-Clinically Frail status (OR = 8.17; 95% CI = 2.71, 24.33) or (b) remaining Moderately Frail (OR = 2.85; 95% CI = 1.51, 5.38).

Given the relatively small number of significant interaction terms, we decided to conduct a follow-up multinomial logistic regression in which we regressed Time 2 latent statuses on baseline risk characteristics. For this analysis, we specified the Not-Clinically Frail status as the reference group. We do not report results for (a) the impact of chronological age on the likelihood of being classified as Mildly Frail or (b) the impact of *APOE* on the likelihood of being classified as Moderately or Mildly Frail, given that these effects varied across baseline statuses (as outlined in the preceding paragraph). As reported in Table 3-11, sex, education, age, clinical cohort, and global cognition were differentially related to the likelihood of being classified as Mildly Frail, Moderately Frail, or Severely Frail as compared to Not-Clinically Frail. Specifically, female sex (OR = 1.24) and a baseline diagnosis of AD (OR = 1.56) increased risk for classification as Mildly Frail. Older age (OR = 1.08), AD (OR = 2.22), poorer global cognitive function (OR = 0.94), and increasing education (OR = 1.04) increased risk for the Moderately Frail status. Finally, older age (OR = 1.08), AD (OR = 2.16), and poorer global cognition (OR = 0.88) increased risk for being classified as Severely Frail.

Discussion

The current study assembled baseline and 2-year follow-up multi-morbidity data from the NACC for a sample of 3,074 older adults with a baseline diagnosis of aMCI or AD. We

subsequently applied data-driven, data-reduction techniques to these indicators and identified the following frailty-related domains of aging morbidity: ambulatory ability, emotional well-being, behavioral disturbances, instrumental health, and cardiovascular symptoms. The proportion of deficits accumulated in each domain (at both time points) was calculated for each participant and used as continuous observed indicators in latent transition analysis (LTA)— a longitudinal extension of latent profile/class analysis that can model change in latent classifications over time. This analytical approach represents a promising alternative to conventional methods for modeling heterogeneity in frailty emergence and progression (e.g., latent growth curve analysis) as it allows researchers to (a) identify distinct clusters of aging morbidity across multiple measurement occasions, (b) determine whether certain statuses may portend a poorer prognosis for frailty progression, and (c) identify risk characteristics that predict baseline status membership and patterns of frailty transitions. Despite these advantages, limited longitudinal epidemiological research has leveraged LTA to examine these research aims, particularly with cognitively impaired samples, and several recent reviews have issued a call for increased systematic research on this topic (Kojima et al., 2019; Rohrmann, 2020; Welstead et al., 2020). The current study was designed to fill these gaps.

RG1: Latent transition analysis

We distinguished two mutually exclusive baseline frailty statuses including the predominant Not-Clinically Frail (*n* = 2,790; 91%) and a smaller Moderately Frail (*n* = 284; 9%) subgroup. At Time 2, we again detected the Not-Clinically Frail (*n* = 1,714; 56%) and Moderately Frail (*n* = 571; 19%) statuses, but at this later time point we also detected two additional statuses representing participants who were Mildly Frail (*n* = 654; 21%) and those who were Severely Frail *(n* = 135; 4%). This expansion of frailty classifications (from moderate only to mild, moderate, and severe)

and accumulation of frailty groups (from 1 to 3 and from 9% to 44% of the sample) in the 2-year interval between the first and second measurement occasion clearly reflects the net progression of study participants towards a higher frailty burden in a relatively brief period. Notably, the Not-Clinically Frail status had the highest prevalence at both time points and was over 50% at the second occasion. This observation of substantial stability in non-frail status accords with previous cross-sectional research conducted with cognitively normal older adults (Bohn et al., 2021; Liu et al., 2017; Looman et al., 2018; Olaya et al., 2017; Sadiq et al., 2018) and adds to the growing literature suggesting that frailty and cognitive impairment are related concepts that mutually interact but may not inevitably co-occur (Burt et al., 2019; Kojima et al., 2017; Robertson et al., 2013). In the current study, Not-Clinically Frail participants were characterized by comparatively less impairment across the observed indicators and the lowest values on an independently calculated 43-item frailty index, whereas participants who were Mildly or Moderately Frail endorsed successively higher levels of aging morbidity, particularly in terms of ambulatory ability, and progressively higher values on the frailty index. The Severely Frail status was characterized by pronounced ambulatory impairment and a tendency for poorer instrumental health. Further, these participants demonstrated the highest burden of frailty on the 43-item index.

Our finding that the detected latent statuses were largely ordered along a continuum representing successively higher levels of ambulatory impairment converges with previous work identifying mobility deficits as a defining characteristic of data-driven frailty profiles or statuses (Bohn et al., 2021; Chhetri et al., 2017; Liu et al., 2017; Sarksian et al., 2008; Sourial et al., 2012). For example, results from the LTA conducted by Lafortune and colleagues (2009) revealed that older adults who were classified as *relatively healthy* endorsed the lowest levels of accumulated aging multi-morbidity whereas the remaining statuses were differentiated according to the severity

of deficits accumulated in the cognitive domain, mobility disability, and impairment in instrumental health. Similarly, in Study 1 of the dissertation research (Bohn et al., 2021), we applied latent profile analysis to cross-sectional multi-morbidity data for a large sample of cognitively normal older adults and reported that participants with *mobility-type frailty* differed from participants who were *not-clinically frail* in that they experienced pronounced mobility impairment and higher values on a 50-item frailty index. The current study extends these results by detecting similarly nuanced longitudinal frailty statuses in clinical cohorts of older adults with a baseline diagnosis of aMCI or AD. Taken together, the foregoing pattern of results suggest that mobility impairment— or more broadly, ambulatory impairment, which represents the extent to which an individual is able to walk unassisted— is a critical component of differentiable frailty subtypes across the spectrum of normal cognitive aging, impairment, and dementia.

Notably, findings from recent cross-sectional research bolsters this claim. Specifically, Yuan et al. (2021) applied multiple-group latent class analysis to baseline multi-morbidity data for 871,801 nursing home residents with normal cognition, MCI, AD, or non-AD dementia. The considered indicators (n = 7) were drawn from the FRAIL-NH scale (Theou et al., 2016), which includes markers related to fatigue, resistance, ambulation, incontinence, weight loss, nutritional status, and help with getting dressed. Findings showed that, for each cohort, a three-class solution representing *mild physical frailty*, *moderate physical frailty*, and *severe physical frailty* provided the best fit to the data. Convergent with present study, participants classified as having moderate or severe physical frailty reported greater mobility dysfunction (e.g., needing physical assistance to transfer between locations in the nursing home) as compared to participants with mild physical frailty. Further, participants with severe physical frailty were more likely to report both urinary and bowel incontinence relative to participants with moderate physical frailty. It is interesting that the

class distinctions and subsequent interpretations reported in Yuan et al. overlap with our own, given that we assembled longitudinal data for wider range of domains of aging morbidity. That is, although we also considered the proportion of deficits participants had accumulated in emotional, behavioral, and cardiovascular domains, these systems did not emerge as defining characteristics of the data-driven frailty statuses. Notably, a similar pattern was detected in Study 1 (Bohn et al., 2021), in that frailty profiles were not differentiated based on the pattern and severity of deficits accumulated in emotional well-being, comorbidity, and cardiac symptoms. A potential explanation for these findings is that— because mobility relies on multiple systems working together in a coordinated and integrated fashion (e.g., musculoskeletal, nervous, cardiovascular, and sensorial systems)— deficits in this domain may account for numerous medical conditions or comorbidities (Montero-Odasso et al., 2009). For this reason, it has been suggested that mobility-related subtypes may better capture heterogeneity in the health status of frail older adults as compared to the proportion of deficits accumulated in related domains of aging morbidity (Montero-Odasso et al., 2009). Future studies could examine the generalizability of these results across a wider range of frailty domains, clinical cohorts, and follow-up durations.

As noted in our review, previous research indicates that frailty may be a dynamic process, characterized by multidirectional trajectories of frailty progression or recurrent transitions between frailty states over time (O'Caoimh et al., 2018; Rohrmann, 2020; Welstead et al., 2020). Importantly, however, the majority of these studies have examined frailty progression in cognitively normal older adults and employed the physical frailty phenotype (Fried et al., 2001) or frailty index (Mitnitski et al., 2001) as the operational definition of frailty. To our knowledge, this study is the first to distinguish and subsequently track longitudinal data-driven frailty statuses across a two-year study interval in a cognitively impaired sample. Our results indicated that, across

clinical cohorts, 61% of the participants who were classified as Not-Clinically Frail at baseline remained in this status at follow-up. Analogous findings were reported by Lafortune and colleagues (2009), in that 66% of the participants who were classified as relatively healthy at baseline remained in this status at the second measurement occasion. After stability, the most common transition pattern for Not-Clinically Frail participants in the current study was towards the neighbouring frailty status— Mildly Frail (21%). A relatively small proportion of Not-Clinically Frail participants transitioned towards statuses representing a marked increase in frailty burden, including Moderately (15%) or Severely Frail (4%). Conversely, the latter two transitions were amongst the most common for participants who were classified at baseline as Moderately Frail. Specifically, 55% of the participants who were classified as Moderately Frail at baseline remained in this status at follow-up and 21% progressed towards the status representing the highest frailty burden— Severely Frail. Similarly, Lafortune et al. reported that, of the participants who were classified as cognitively and physically impaired at baseline, 52% remained in this status at follow-up and 25% died. Interestingly, our results indicated that a subset of Moderately Frail participants regressed to the Mildly (17%) or Not-Clinically Frail (7%) status, suggesting that reversion of frailty is possible in aging characterized by aMCI or AD. This is an important finding. Several recent reviews have highlighted that spontaneous clinical remission of frailty remains scarcely considered and identified this as a priority area (Canevelli et al., 2017; Ofori-Asenso et al., 2019). At least one other study examined progression of the physical frailty phenotype in a sample of community dwelling older adults with baseline diagnoses of MCI or AD and reported that, across a 1-year study duration, 32% of the study sample evinced frailty regression (e.g., frail to pre-frail, pre-frail to robust; Chong et al., 2015).

It is important to note, however, that while our results suggest that Moderately Frail cognitively impaired older adults may improve their frailty status (to Not-Clinically Frail or Mildly Frail), these transitions (a) were comparatively less likely than stability or forward progression and (b) were less likely for participants who were classified at baseline as Moderately versus Not-Clinically Frail. Collectively, these results suggest that, once the disabling cascade of frailty is fully established, reversing or attenuating this process may become increasingly challenging (Canevelli et al., 2017). Similarly, longitudinal studies examining trajectories of disability or functional limitations have reported that individuals presenting with higher levels of baseline impairment have a decreased probability of recovery and an increased probability of decline or adverse outcomes (Kim et al., 2021; Zacarías-Pons et al., 2021). Together, these data highlight the potential importance of early interventions. Specifically, our results suggest that ambulatory impairment should be targeted and tracked in clinical and research settings. Future studies could examine whether rehabilitation and pharmacologic treatment targeting these deficits may offset, reverse, or delay frailty progression and related negative outcomes (Apóstolo et al., 2018).

Consistent with the present study, accumulating evidence suggests that mobility impairment may represent a harbinger of adverse frailty transitions or trajectories. For example, Fallah and colleagues (2011) reported that the probability of transitioning between frailty states over time was predicted by performance on a rapid gait test, such that participants with poorer mobility function were less to remain stable or improve at 18-month, 36-month, and 54-month follow-up as compared to participants with better mobility function. More recently, Vergehese et al. (2021) assembled longitudinal data for a 41-item frailty index and distinguished the following trajectories in a sample of cognitively normal older adults: *relatively stable*, *mild frailty*, *moderate frailty*, and *severely frail*. Of relevance to the current research, each of the respective trajectories were

characterized by successively higher levels of baseline impairment in completing a timed walk task, leading the authors to suggest that future examinations of risk and prognostic factors for frailty progression should incorporate mobility indicators. Towards this end, in Study 1 (Bohn et al., 2021) we demonstrated that older adults with mobility-type frailty evinced more rapid and widespread deficit accumulation as compared to older adults without such recorded deficits. Similarly, Montero-Odasso and colleagues (2009) assembled baseline mobility indicators (n = 11) for a large sample of frail older adults and distinguished three profiles representing *mild*, *moderate*, and *severe mobility impairment*. These profiles were subsequently validated against prediction of adverse frailty-related outcomes. Results indicated that older adults with severe mobility impairment were approximately two to three times as likely to die or be placed in a nursing home, respectively, as compared to older adults with mild or moderate mobility impairment. These associations remained significant after adjusting for age, sex, clinical cohort (self-reported memory impairment or dementia), disability in activities of daily living, and medical comorbidities. Further, follow-up analyses verified that mobility profiles were stronger predictors of adverse outcomes as compared to single indicators. We advance this prior work by (a) modeling progression of data-driven frailty statuses characterized by varying levels of ambulatory impairment and (b) identifying predictors that may elevate risk for classification into statuses characterized by a higher frailty burden or worse transition patterns.

RG2: Prediction of baseline membership and transition probabilities

We characterized and validated the detected latent statuses by examining non-modifiable and potentially modifiable risk factors as predictors of (a) baseline membership and (b) the probability of transitioning across frailty statuses. Results from the former analysis revealed that sex, age, clinical cohort, and global cognition were associated with baseline frailty classifications. In

contrast to our expectations, findings from the latter analysis revealed that only a small number of frailty transitions varied as a function of the considered predictors, including age and *APOE* carrier status. Although these null results are consistent with the literature on LTA (e.g., Collins & Lanza, 2010) and previous studies employing this analytical approach (e.g., Ryoo et al., 2018), for now, we note this as a potential study limitation. Specifically, it is possible that for the present frailty phenomena, the predictors we selected on the basis of previous literature and availability in the NACC database were not in fact among the controlling factors. Accordingly, in future analyses, we plan to re-review the NACC database and identify candidate risk and protection factors that may be differentially associated with frailty progression. For example, because ambulation is a complex process that requires intact function and coordination between multiple aging systems, including neuropsychological (e.g., attention, executive function), sensorial, cardiopulmonary, and musculoskeletal systems (Chhetri et al., 2017; Montero-Odasso et al., 2009), we will look for variables representing these domains. Further, following from previous research suggesting that impaired mobility and cognitive function may share common risk factors and pathways, including chronic inflammation, hormonal dysregulation, nutritional deficiencies, and reduced physical activity (see Chhetri et al., 2017 for a review), we will also examine the NACC database for indicators representing these domains. In the interim, we conducted a follow-up analysis in which we examined baseline risk characteristics as predictors of latent status membership at Time 2. Consistent with the foregoing pattern of results, sex, age, clinical cohort, and global cognition differentiated Not-Clinically Frail participants from the remaining statuses. Findings for each of the respective predictors are discussed in turn below. Education played a minimal role in prediction analyses, with results indicating that higher levels increased odds for the Moderately Frail as compared to Not-Clinically Frail status. Given the unexpected direction of this effect (Chang et al.,

2013; Welstead et al., 2020; Zacarías-Pons et al., 2021) and the fact that educational background is often not considered in relation to data-driven frailty profiles (Bohn et al., 2021; Lafortune et al., 2009; Yuan et al., 2021), we plan to statistically control for education in future analyses (Chong et al., 2015; Verghese et al., 2021).

With respect to sex, our results indicated that, at baseline, females were more likely to be classified as Not-Clinically Frail and males were more likely to be classified as Moderately Frail. This pattern runs in contrast to Study 1 findings (Bohn et al., 2021), where we reported that sex was equally related to the likelihood of being classified into data-driven frailty profiles. Importantly, we reasoned that sex differences may be more likely to appear in later life or in more serious frailty conditions. Findings from the current study and Lafortune et al. (2009) buttress this notion. Specifically, NACC participants were comparatively older (NACC *M*age = 74.70; VLS *M*age = 70.61) and frailer (NACC frailty index *M* = 0.23; VLS frailty index mean = 0.13) than Study 1 participants. Similarly, Lafortune and colleagues characterized their study sample as frail old-old adults (*M*age = 82 years) and reported that females were more likely to be classified as relatively healthy at baseline and males were more likely to be classified into a latent status characterized by mobility and functional limitations. Further, the authors reported descriptive differences in latent transition probabilities across sex (i.e., no significance tests were reported), such that males were more likely to remain stable and females were more likely to transition towards frailty statuses representing a higher level of impairment. Although we did not find that latent transition probabilities varied significantly across sex, results from our follow-up analysis are generally consistent with the preceding pattern. Specifically, we found that (a) the odds of being classified as Mildly Frail were greater for females as compared to males and (b) sex was equally related to the likelihood of being classified as Moderately or Severely Frail. The latter finding

indicated that female sex was no longer a protection factor and implied that females may have had a general tendency to advance towards statuses characterized by a higher frailty burden. Relatively limited research has examined sex differences in frailty subtype membership or progression and the findings reported are equivocal (Garre-Olmo et al., 2013; Lafortune et al., 2009; Looman et al., 2018; Yuan et al., 2021; Zhang et al., 2020). Similarly, recent systematic reviews have highlighted that the sparse literature examining sex differences in frailty index or phenotype progression have reported inconsistent findings (Kojima et al., 2019; O'Caoimh et al., 2018; Welstead et al., 2020). As such, we identify this as an important area of continued research interest (Thibeau et al., 2019).

Results for chronological age were consistent with previous variable-centered (Kojima et al., 2019; O'Caoimh et al., 2018; Welstead et al., 2020) and person-centered (Bandelow et al., 2016; Lafortune et al., 2009; Liu et al., 2017; Sadiq et al., 2018; Tomás et al., 2020) research identifying older age as a risk factor for frailty, including classification into data-driven clusters characterized by greater impairment. For example, Yuan et al. (2021) reported that, across clinical cohorts of older adults with normal cognition, MCI, AD, and non-AD dementia, older age was associated with higher odds of belonging to the moderate or severe physical frailty classes as compared to mild physical frailty. In our study, we found that older age increased risk for assignment into the Moderately or Severely Frail status at each time point. Notably, the effects of chronological age on the likelihood of transitioning to the Mildly as compared to Not-Clinically Frail status varied across baseline statuses. Specifically, amongst Not-Clinically Frail participants, older age increased the likelihood of progressing towards the Mildly Frail status. Conversely, age was unrelated to this transition probability for Moderately Frail participants. These differential effects suggest that, early in the clinical course of frailty, older age may exacerbate risk for frailty progression; however, in the moderate stages of frailty progression, younger age may not operate as a protection factor.

Because Lafortune and colleagues (2009) statistically controlled for the effects of age in their LTA, this study is the first to our knowledge to examine whether longitudinal frailty classifications vary as a function of this risk characteristic. Future studies are required to advance understanding of the impact of chronological age on data-driven frailty transitions.

As expected, a baseline diagnosis of AD and poorer global cognitive function each increased the odds of being classified as Moderately Frail at the first measurement occasion. At follow-up, results indicated that participants who were classified as having AD at baseline were between 1.6–2.2 times as likely as participants with aMCI to be characterized as Mildly, Moderately, or Severely Frail. A similar pattern was detected for global cognition, in that poorer performance increased risk for the Moderately or Severely Frail statuses. This study is the first to our knowledge to examine the conditional effects of clinical cohort *and* global cognitive function on data-driven frailty classifications. In contrast, much of the available research has operationalized cognitive status (or clinical cohort) using summary measures of global cognitive function (e.g., MMSE; Bandelow et al., 2016; Bekić et al., 2019; Majnarić et al., 2020), which may be limited in diagnostic and clinical utility due to low sensitivity and specificity (Arevalo-Rodriguez et al., 2015). Of relevance to the present results, Yuan et al. (2021) collapsed across clinical cohort (i.e., normal, MCI, AD, non-AD dementia) and reported that successively higher levels of cognitive impairment (none/mild, moderate, and severe) increased risk for assignment into moderate or severe physical frailty classes. They did not report whether frailty classification varied as a function of baseline diagnoses. We advance this limited prior work by (a) demonstrating that clinical cohort and severity of cognitive impairment each increased risk for statuses representing a higher frailty burden and (b) suggesting that these indicators should be tested as dissociable features in future data-driven research.

We were initially surprised to find that latent transition probabilities did not vary as a function of the above-mentioned risk characteristics, given that previous studies have demonstrated that clinical cohort (Buchman et al., 2013, 2014; Trevisan et al., 2017) and global cognition (Lee et al., 2014; Mendonça et al., 2020; Nari et al., 2021) affect frailty transitions and trajectories. Notably, Chong and colleagues (2015) reported that frailty phenotype transitions did not vary across subgroups of older adults with MCI or AD, nor as a function of global cognitive performance. Importantly, however, when the sample was stratified on the basis of clinical cohort, results indicated that global cognition was unrelated to frailty progression in MCI, whereas declining global cognition predicted frailty progression in mild-to-moderate AD. These results suggest that significant predictor effects may be more likely to appear in subgroup analyses. Accordingly, we stratified the sample on the basis of clinical cohort (aMCI, AD), race/ethnicity (non-Hispanic White, Black/African American), and/or sex (male/female). For each stratification, we then performed a series of follow-up LTA in order to test whether the detected latent statuses and transition patterns varied as a function of these characteristics. Results indicated issues with model non-convergence and/or a lack of longitudinal measurement invariance. As such, we note this as both a potential study limitation and an important target for follow-up analyses (e.g., examine prediction patterns as stratified by sex).

APOE ε4 carrier status was unrelated to frailty classifications at each time point. Importantly, however, examination of conditional latent transition probabilities indicated that a subset of *APOE* effects varied across baseline frailty statuses. Follow-up analyses indicated that (a) Not-Clinically Frail participants who carried the ε4 risk allele were more likely to remain in this status at follow-up as compared to advancing towards the Mildly or Moderately Frail statuses and (b) Moderately Frail participants who carried the risk allele more likely to be reclassified as Mildly Frail as

compared to Not-Clinically Frail or remaining Moderately Frail. This pattern suggests that, early in the clinical course of frailty, carriers of the ε4 allele may be at a reduced risk for frailty status progression, whereas in the moderate stages of frailty, carriers of the ε4 allele may be more likely to experience frailty reversion. In the broader area of brain and cognitive aging, the ε4 allele is an established risk factor for exacerbated cognitive decline, MCI, and AD (Liu et al., 2013; Schiepers et al., 2012). Conversely, the literature examining *APOE*-frailty associations is sparse and the findings are equivocal (Bai et al., 2021; Rockwood et al., 2008; Thibeau et al., 2019; Ward et al., 2021a). Nevertheless, at least one other frailty-related study indicated a possible protective effect of the ε4 allele (Kulminski et al., 2008). Specifically, Kulminski and colleagues analyzed sex-specific associations between *APOE* isoforms and impairment in activities of daily living and reported that (a) female carriers of the ε4/ε4 allele had a five-fold decreased risk for severe impairment in activities of daily living as compared to non-carriers and (b) there were no ε4/ε4 male carriers with disabilities. At present, the reasons for these associations remain unclear as does the generalizability of this pattern of results. These questions could be addressed in future studies.

Strengths and limitations

We acknowledge several methodological strengths and limitations. First, we used a substantial and well-characterized sample of participants from the NACC. Eligible study participants contributed longitudinal multi-morbidity data and were diagnosed at baseline as having aMCI or AD based on prevailing clinical diagnostic criteria (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). By excluding participants who were cognitively normal at baseline, we were able to (a) avoid the simple clustering of participants into frailty statuses representing impaired cognitive function and (b) identify and track significant heterogeneity in frailty emergence and progression in a cognitively impaired sample. At the same time, we recognize that

our results may be limited in generalizability to cognitively normal older adults. Previous cross-sectional research reported that data-driven frailty classes were invariant across clinical cohorts of older adults with normal cognition, MCI, AD, or non-AD dementia (Yuan et al., 2021). Nevertheless, we encourage future longitudinal epidemiological studies to explicitly test this research aim.

Second, we examined our central research questions using data-driven and person-centered analytical techniques. In our review, we identified only one other study that examined frailty emergence and progression using LTA (Lafortune et al., 2009). We advance this prior research by assembling longitudinal big data for a wider range of (a) clinical cohorts, (b) aging morbidity indicators, and (c) non-modifiable or potentially modifiable risk characteristics. Our results have applications to precision intervention and treatment protocols by advancing understanding of frailty statuses that may portend a poorer clinical prognosis and the types of characteristics that individuals comprising an at-risk frailty status may possess. We selected this analytical approach on the basis of literature indicating that LTA boasts several advantages over conventional approaches to detecting homogenous subgroups (e.g., cluster analysis) or modeling longitudinal change trajectories (e.g., latent growth curve analysis). With respect to the former, LTA provides (a) model-based participant classifications, (b) statistical diagnostic tools that elucidate the quality of participant classifications, and (c) information-theoretic indices that promote selection of the most parsimonious model (thus discouraging overfitting; Muthén & Muthén, 2000). Regarding the latter, LTA includes features that allow researchers to model multidimensional constructs (such a frailty; Clegg et al., 2013) and elucidate (a) multi-directional patterns of transitions and (b) the effect of predictor variables on membership and progression (Lanza & Collins, 2008). It is important to note, however, that we performed prediction analyses using participants' most likely

latent status at each time point. A potential limitation of this approach is that it does not account for uncertainty (or error) in latent classifications. Nevertheless, the "classify-analyze" approach has demonstrated utility for modeling complex developmental constructs (Bray et al., 2015; Nylund-Gibson et al., 2014; Seaton et al., 2012; Wong et al., 2012) and can be readily applied in LTA models characterized by large sample sizes and high classification accuracy (Asparouhov & Muthén, 2014; Clark & Muthén, 2009). The current study meets these criteria.

Third, we assembled longitudinal data for multi-morbidity indicators representing the heterogeneity of frailty. This allowed us to distinguish nuanced frailty statuses across two measurement occasions and identify ambulatory impairment as a harbinger of adverse frailty transitions. We note, however, that the domains of aging morbidity considered in the current study do not span the full range deficits that an older adult may accumulate. For example, in Study 1 we also included respiratory symptoms and diseases and identified *respiratory-type frailty* as amongst one the three profiles representing early aging morbidity (Bohn et al., 2021). Due to unavailability, we were unable to consider such indicators in the present study. This is a recurring issue in frailty research. Much of the available literature on frailty transitions and trajectories have employed the physical frailty phenotype or frailty index as the operational definition of frailty (O'Caoimh et al., 2018; Welstead et al., 2020). Notably, the former approach considers a restricted number of phenotypes, whereas the latter approach considers no phenotypes, but rather a composite score that may vary as a function of the considered indicators. Nevertheless, future work could explore whether inclusion of deficits not considered in the present research may elucidate frailty statuses and patterns of progression that diverge from those we report.

Conclusions

In the current study, we identified and tracked data-driven frailty statuses representing varying levels of accumulated aging multi-morbidity in a large sample of cognitively impaired older adults, including Not-Clinically Frail, Mildly Frail, Moderately Frail, and Severely Frail. Whereas the former status was comprised of participants with relatively limited impairment across the considered domains of aging morbidity, the latter three statuses were comprised of individuals with successively higher levels of ambulatory impairment and frailty burdens. Latent transition analyses indicated that participants who were Not Clinically-frail at baseline had a high probability of remaining in relatively better health at a two-year follow-up. In contrast, participants who were classified as Moderately Frail at baseline had a high probability of endorsing moderate-to-high levels of impairment at follow-up and a comparatively lower likelihood of frailty reversion. Collectively, these results indicate that ambulatory impairment should be targeted and tracked in clinical-research settings. It is possible that early interventions targeting this domain of aging morbidity may offset or delay frailty emergence and progression. This question could be tested in future studies. Results from our prediction analyses highlighted that (a) select non-modifiable and potentially modifiable risk characteristics were associated with classifications into data-driven frailty statuses at each time point and (b) we need to re-examine the NACC database and conduct follow-up analyses in order to identify significant predictors of latent transition probabilities. In future studies, we plan to also examine the detected latent statuses as predictors of related outcomes, including falls, hospitalization, and institutionalization.

Table 3-1. *Participant Characteristics at Baseline*

Characteristic	Total Sample	aMCI	AD	Sig.
n(%)	3,074	878 (29%)	2,196 (71%)	
Total n of in person visits	4.50 (1.77)	4.97 (1.97)	4.31 (1.65)	***
Inter-wave interval (in days)	780.01 (78.88)	788.48 (79.69)	776.62 (78.32)	***
n(%) female	1,603 (52%)	411 (47%)	1,192 (54%)	***
Age (in years)	74.70 (8.69)	74.53 (7.52)	74.76 (9.12)	*ns*
Education (in years)	15.08 (3.37)	16.08 (3.12)	14.68 (3.37)	***
n(%) non-Hispanic White	2,782 (91%)	802 (91%)	1,980 (90%)	*ns*
n(%) married	2,215 (72%)	639 (73%)	1,576 (72%)	*ns*
n(%) in private residence	2,795 (91%)	806 (92%)	1,989 (91%)	*ns*
MMSE [a]	23.34 (4.73)	27.02 (2.41)	21.89 (4.63)	***
Global CDR	0.79 (0.42)	0.50 (0.10)	0.91 (0.44)	***
n(%) *APOE* ε4 [b]	1,536 (58%)	395 (53%)	1,141 (60%)	**
Frailty Index	0.23 (0.12)	0.15 (0.09)	0.27 (0.12)	***

Note. aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; Sig, significance; MMSE, Mini-Mental State Exam; CDR, Clinical Dementia Rating Scale; *APOE*, Apolipoprotein E. Results presented as mean (standard deviation) or *n*(%) of the sample with the associated characteristic. *p*-values are based on independent sample *t*-tests or chi-square tests, as appropriate. Scores on the CDR are interpreted such that 0 = *no impairment*, 0.5 = *questionable impairment*, 1 = *mild impairment*, 2 = *moderate impairment*. 3 = *severe impairment*. [a] A subset of each sample was administered the Montreal Cognitive Assessment (MoCA) in lieu of the MMSE; education-adjusted scores on the MoCA were converted to an equivalent MMSE score using published conversion tables derived from the National Alzheimer's Coordinating Center Uniform Data Set (Monsell et al., 2016). [b] Results are based on 746 participants with aMCI and 1,903 participants with AD who were genotyped.

*** $p < .001$ ** $p < .01$ * $p < .05$

Table 3-2. *Complete List of 59 Candidate Multi-Morbidity Items Drawn from the Uniform Data Set*

	Multi-Morbidity Item	Coding
SR or CE	Heart attack or cardiac arrest *	0 = no; 1 = yes
	Atrial fibrillation *	
	Carotid procedure: angioplasty, endarterectomy, or stent *	
	Pacemaker and/or defibrillator *	
	Congestive heart failure *	
	Stroke *	
	Parkinson's disease	
	Diabetes *	
	Hypertension *	
	Hypercholesterolemia	
	Vitamin B 12 deficiency	
	Thyroid disease *	
	Urinary incontinence	
	Bowel incontinence	
SR	Number of medications *	0 = 0-3; 0.5 = 4-7; 1 = 8+
CE	Vision functionally normal without corrective lenses *	0 = yes; 1 = no
	Hearing functionally normal without hearing aid *	
CE	Vision functionally normal with corrective lenses *	0 = N/A, yes; 1 = no
	Hearing functionally normal with hearing aid *	
CE	Difficulty writing checks, paying bills, or balancing a check book	0 = normal, N/A; 0.33 = difficulty, but independent; 0.66 = requires assistance; 1 = dependent [a]
	Difficulty assembling tax records, business affairs, or other papers	
	Difficulty shopping alone for clothes, household necessities, or groceries *	

	Difficulty playing a game of skill such as bridge or chess, working on a hobby *	
	Difficulty heating water, making a cup of coffee, turning off the stove *	
	Difficulty preparing a balanced meal *	
	Difficulty keeping track of current events	
	Difficulty paying attention to and understanding a TV program, book, or magazine *	
	Difficulty remembering appointments, family occasions, holidays, medications	
	Difficulty traveling out of the neighborhood, driving, or arranging to take public transportation *	
CE	Walking changed not due to injury or arthritis	0 = no; 1 = yes
	Falls more than usual	
	Tremor	
	Slowing of motor movements	
CE	Engages in repetitive activities (pacing, handling buttons, wrapping string)	0 = no, N/A; 1 = yes [b]
	Nighttime behaviors: awakens in the night, rises too early, excessive naps *	
	Appetite: changes in weight or food preferences	
	Delusions	
	Hallucinations	
	Agitation and/or aggression	
	Depression and/or dysphoria*	
	Anxiety	
	Agitation and/or aggression	
	Apathy and/or indifference	

	Elation and/or euphoria	
	Irritability and/or lability	
	Disinhibition	
M	Resting heart rate (bpm) *	0 = 60-99; 1 = < 60 or 100+
M	Pulse pressure (mmHg) *	0 = 32.13-63.90; 0.5 = 64-75.9; 1 = < 32.13 or 76+
M	Body mass index (kg/m^2) *	0 = 18.5-25; 0.5 = 25.1 to < 30; 1 = < 18.5 or ≥ 30
SR	Dropped many activities and interests *	0 = no; 1 = yes [c]
	Feel that life is empty *	
	Often get bored *	
	Afraid something bad is going to happen to you	
	Often feel helpless *	
	Prefer to stay home rather than going out and doing new things *	
	Feel worthless *	
	Feel that your situation is hopeless *	
	Feel that most people are better off than you *	
SR	Feel full of energy *	0 = yes; 1 = no [c]
	Basically satisfied with life *	

Note. SR, self-reported; CE, clinician evaluated; M, measured. * Denotes items that are comparable to those used in Bohn et al. (2021) to calculate a frailty index. [a] Reported as change over the past four weeks; [b] Item from the Neuropsychiatric Inventory Questionnaire; [c] Item from the Geriatric Depression Scale.

Table 3-3. *List of Variables Submitted to Exploratory Factor Analysis and Used to Construct an Independent 43-Item Frailty Index*

	Multi-Morbidity Item	Coding
SR or CE	Stroke	0 = no; 1 = yes
	Diabetes	
	Hypertension	
	Hypercholesterolemia	
	Urinary incontinence	
	Bowel incontinence	
SR	Number of medications	0 = 0-3; 0.5 = 4-7; 1 = 8+
CE	Difficulty writing checks, paying bills, or balancing a check book	0 = normal, N/A; 0.33 = difficulty, but independent; 0.66 = requires assistance; 1 = dependent [a]
	Difficulty assembling tax records, business affairs, or other papers	
	Difficulty shopping alone for clothes, household necessities, or groceries [*]	
	Difficulty playing a game of skill [*]	
	Difficulty heating water, making a cup of coffee, turning off the stove [*]	
	Difficulty preparing a balanced meal [*]	
	Difficulty keeping track of current events	
	Difficulty paying attention to/understanding TV program, book, magazine [*]	
	Difficulty remembering appointments, family occasions, holidays, medications	

	Difficulty traveling out of the neighborhood, driving, or arranging to take public transportation *	
CE	Walking changed not due to injury or arthritis	0 = no; 1 = yes
	Falls more than usual	
	Tremor	
	Slowing of motor movements	
CE	Engages in repetitive activities (pacing, handling buttons, wrapping string)	0 = no, N/A; 1 = yes [b]
	Nighttime behaviors: awakens in the night, rises too early, excessive naps *	
	Appetite: changes in weight or food preferences	
	Delusions	
	Depression and/or dysphoria*	
	Anxiety	
	Agitation and/or aggression	
	Apathy and/or indifference	
	Irritability and/or lability	
	Disinhibition	
M	Body mass index (kg/m^2)	0 = 18.5-25; 0.5 = 25.1 to < 30; 1 = < 18.5 or ≥ 30
SR	Dropped many activities and interests	0 = no; 1 = yes [c]
	Feel that life is empty	

	Often get bored	
	Afraid something bad is going to happen to you	
	Often feel helpless	
	Prefer to stay home rather than going out and doing new things	
	Feel worthless	
	Feel that your situation is hopeless	
	Feel that most people are better off than you	
SR	Feel full of energy	0 = yes; 1 = no [c]
	Basically satisfied with life	

Note. SR, self-reported; CE, clinician evaluated; M, measured. [a] Reported as change over the past four weeks; [b] Item from the Neuropsychiatric Inventory Questionnaire; [c] Item from the Geriatric Depression Scale.

Table 3-4. *Multi-Morbidity Items (n* = 33) *by Exploratory Factor Analysis Derived Domains*

Domain	Indictor
Ambulatory Ability	Bowel incontinence
	Urinary incontinence
	Slowing of motor movements
	Tremor
	Walking changed not due to injury or arthritis
Emotional Wellbeing	Satisfied with life
	Often feel helpless
	Prefer to stay home
	Often get bored
	Dropped many activities and interests
Behavioral Disturbances	Disinhibition
	Irritability and/or lability
	Apathy and/or indifference
	Agitation and/or aggression
	Anxiety
	Depression and/or dysphoria
	Appetite: changes in weight or food preferences
	Engages in repetitive activities
	Nighttime behaviors
Instrumental Health	Difficulty traveling out of the neighborhood
	Difficulty remembering appointments
	Difficulty paying attention to TV program
	Difficulty keeping track of current events
	Difficulty preparing a balanced meal
	Difficulty turning off the stove
	Difficulty playing a game of skill
	Difficulty shopping alone
	Difficulty assembling tax records

	Difficulty paying bills
Cardiovascular Symptoms	Total number of medications
	Hypercholesterolemia
	Hypertension
	Diabetes

Table 3-5. *Fit Indices for Confirmatory Factor Analysis*

Model	χ^2	*df*	*p*	RMSEA	CFI	TLI
Random subset (50%)						
Time 1	1213.81	485	<.001	.03 (.03 - .03)	.89	.88
Time 2	1337.80	485	<.001	.03 (.03 - .04)	.88	.87
Entire study sample						
Time 1	1794.70	485	<.001	.03 (.03 - .03)	.90	.89
Time 2	2138.87	485	<.001	.03 (.03 - .04)	.87	.86

Note. χ2, chi-square test of model fit; *df*, degrees of freedom for model fit; RMSEA, root mean square error of approximation; RMSEA is shown with 90% confidence intervals; CFI, comparative fit index; TLI, Tucker Lewis Index.

Table 3-6. *Model Fit Indices for Latent Profile Solutions at Each Time Point*

n profiles	-2 *LL*	npar	AIC	BIC	SABIC	LMR	VLMR	Entropy
Model: Time 1								
1	-2,862.42	20	-2822.42	-2701.81	-2765.35	--	--	--
2	**-4,558.66**	**26**	**-4506.66**	**-4349.86**	**-4432.48**	**<.001**	**<.001**	**.99**
3	-6,297.75	32	-6,297.75	-6233.75	-6040.77	.11	.11	1.0
Model: Time 2								
1	610.98	20	650.98	771.60	708.05	--	--	--
2	-511.24	26	-459.24	-302.44	-385.05	<.001	<.001	.91
3	-1,260.28	32	-1196.28	-1003.30	-1104.97	<.001	<.001	.97
4	**-1,640.11**	**38**	**-1564.11**	**-1334.94**	**-1455.68**	**<.001**	**<.001**	**.91**
5	-2,138.66	44	-2050.66	-1,785.31	-1925.117	1.0	1.0	.92

Note. -2 *LL*, -2 log-likelihood; npar, number of parameters free; AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample size adjusted BIC; LMR, adjusted Lo-Mendell-Rubin likelihood ratio test; VLMR, adjusted Vuong-Lo-Mendell-Rubin likelihood ratio test. The best-fitting model is bolded.

Table 3-7. *Model Fit Indices for Longitudinal Measurement Invariance Tests*

	-2 *LL*	npar	AIC	BIC	SABIC	Δ -2*LL*	Δ AIC	Δ BIC
Model 1[a]	-6198.77	64	-6070.77	-5684.80	-5888.16	--	--	--
Model 2[b]	**-6635.85**	**54**	**-6527.85**	**-6202.19**	**-6373.77**	**-437.08**	**-517.39**	**-457.08**
Model 3[c]	-5733.36	39	-5655.36	-5420.16	-5544.08	902.49	782.03	872.50

Note. -2 *LL*, -2 log-likelihood; npar, number of parameters free; AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample size adjusted BIC; Δ, change in the associated parameter. The best-fitting model is bolded. [a] Indicator means were freely estimated across time. [b] Indicator means for Time 1 latent statuses were constrained to equality over time. [c] Indicator means and within status variances were constrained to equality over time.

Table 3-8. *Standardized Mean Differences Across Latent Statuses*

	Latent Status					
Indicator	SEV – MOD	SEV – MILD	SEV – NCF	MOD – MILD	MOD – NCF	MILD – NCF
Cardiovascular symptoms	.05	.09	.43	.05	.43	.38
Instrumental health	.70	.97	**1.47**	.20	.89	.69
Behavioral disturbances	.36	.54	.74	.20	.44	.24
Emotional well-being	.15	.37	.43	.24	.31	.09
Ambulatory ability	**8.98**	**15.20**	**18.70**	**6.96**	**11.27**	**4.63**

Note. SEV, Severely Frail; MOD, Moderately Frail; MILD, Mildly Frail; NCF, Not-Clinically Frail. Model estimated means for the Not-Clinically Frail and Moderately Frail statuses were constrained to equality over time. Indicators are coded such that higher values denote greater impairment. Bolded values represent indicators with a moderate-to-high degree of class separation.

Table 3-9. *Participant Characteristics at Baseline by Time 1 and 2 Latent Status*

	Time 1 Latent Status		Time 2 Latent Status			
Baseline Characteristic	NCF	MODER	NCF	MILD	MODER	SEVERE
n(%)	2,790 (91%)	284 (9%)	1,714 (56%)	654 (21%)	571 (19%)	135 (4%)
Total *n* in person visits	4.53 (1.79)	4.20 (1.46) ***	4.69 (1.89) c	4.50 (1.67) c	4.13 (1.51) d	3.61 (1.01) e, ***
Inter-wave interval (days)	779.81 (78.71)	782.01 (80.65)	778.68 (77.36) c	776.41 (74.95) c	782.32 (84.16) c	804.56 (89.19) d, **
n Female	4,466 (53%)	137 (48%)	876 (51%) c	375 (57%) d	283 (50%) c	69 (51%) c,d **
Age (in years)	74.23 (8.63)	79.25 (7.98) ***	72.72 (8.49) c	76.31 (8.36) d	77.96 (8.22) d	78.19 (7.90) d, ***
Education (in years)	15.12 (3.37)	14.65 (3.43) *	15.27 (3.23) c	14.77 (3.55) d,e	15.07 (3.53) c,d	14.11 (3.38) e ***
n non-Hispanic White	2,531 (91%)	251 (88%)	1,564 (91%)	593 (91%)	508 (89%)	117 (87%)
n married	2,021 (72%)	194 (68%)	1,292 (76%) c	449 (69%) d	386 (68%) d	88 (65%) d, ***
n in private residence	2,552 (92%)	243 (86%) ***	1,584 (94%) c	588 (92%) c,d	505 (90%) d	118 (89%) d, **
MMSE a	23.48 (4.62)	21.98 (5.50) ***	24.04 (4.38) c	23.31 (4.43) d	22.04 (5.16) e	20.05 (5.88) f, ***
Global CDR	0.77 (0.40)	1.02 (0.54) ***	0.71 (0.34) c	0.80 (0.39) d	0.95 (0.50) e	1.09 (0.54) f, ***
n APOE $\varepsilon 4^{+}$ b	1,419 (55%)	117 (49%) **	912 (61%) c	323 (57%) c	234 (49%) d	67 (60%) c, ***
Frailty index	0.22 (0.12)	0.37 (0.12) ***	0.20 (0.11) c	0.25 (0.12) d	0.30 (0.13) e	0.37 (0.13) f, ***

Note. NCF, Not-Clinically Frail; MILD, Mildly Frail; MODER, Moderately Frail; SEVERE, Severely Frail; Sig, significance; MMSE, Mini-Mental State Exam; CDR, Clinical Dementia Rating Scale; *APOE*, Apolipoprotein E. Results presented as mean (standard deviation) or *n*(%) of the sample with the associated characteristic. *p*-values are based on independent sample *t*-tests, one-way ANOVA, or chi-square tests, as appropriate. We adjusted for multiple comparisons using post-hoc Tukey tests or Games-Howell tests as appropriate. Scores on the CDR are interpreted such that 0 = *no impairment*, 0.5 = *questionable impairment*, 1 = *mild impairment*, 2 = *moderate impairment*. 3 = *severe impairment*. [a] A subset of each sample was administered the Montreal Cognitive Assessment

(MoCA) in lieu of the MMSE; education-adjusted scores on the MoCA were converted to an equivalent MMSE score using published conversion tables derived from the National Alzheimer's Coordinating Center Uniform Data Set (Monsell et al., 2016). [b] Results are based on 2,649 participants who were genotyped. [c,d,e,f] Values with different superscripts differ from one another.

*** $p < .001$ ** $p < .01$ * $p < .05$

Table 3-10. *Latent Transition Probabilities Based on the Unconditional Model*

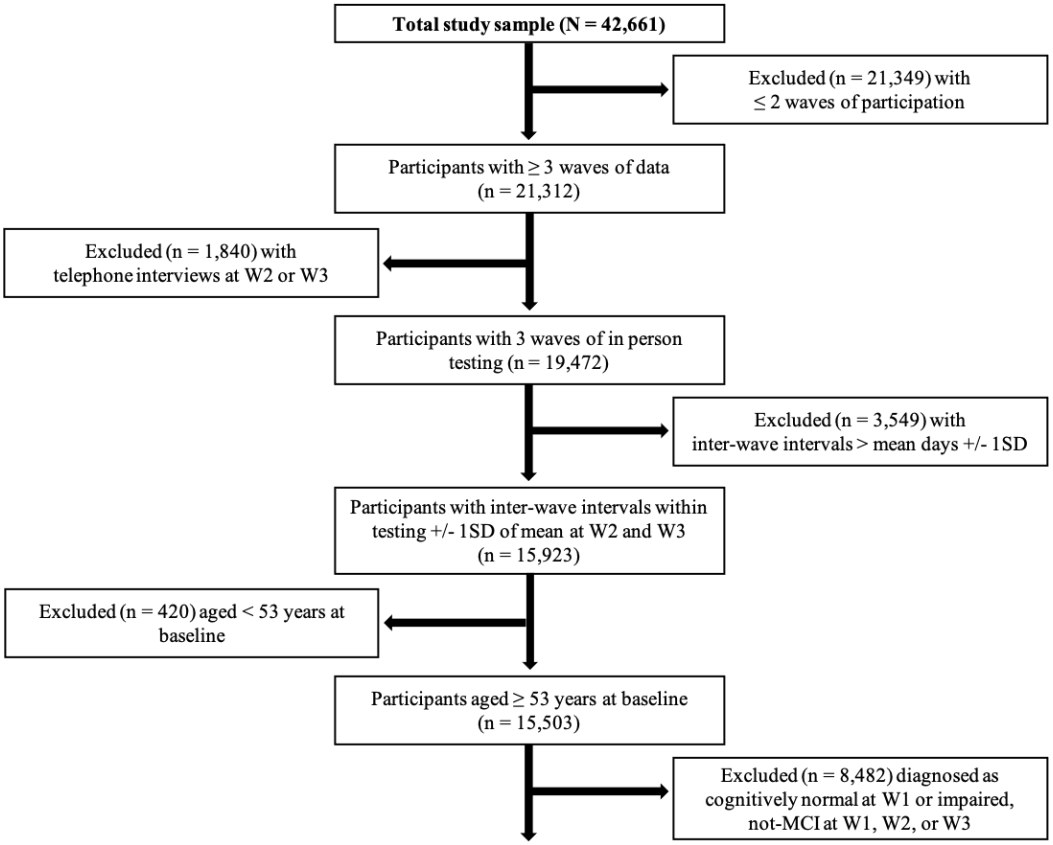
	Time 2 Latent Status			
	Not-Clinically Frail (*n* = 1,714; 56%)	Moderately Frail (*n* = 571; 19%)	Mildly Frail (*n* = 654; 21%)	Severely Frail (*n* = 135; 4%)
Time 1 Latent Status				
Not-Clinically Frail (*n* = 2,790; 91%)	**0.61 (*n* = 1,693)**	0.15 (*n* = 416)	0.21 (*n* = 605)	0.03 (*n* = 76)
Moderately Frail (*n* = 284; 9%)	0.07 (*n* = 21)	**0.55 (*n* = 155)**	0.17 (*n* = 49)	0.21 (*n* = 59)

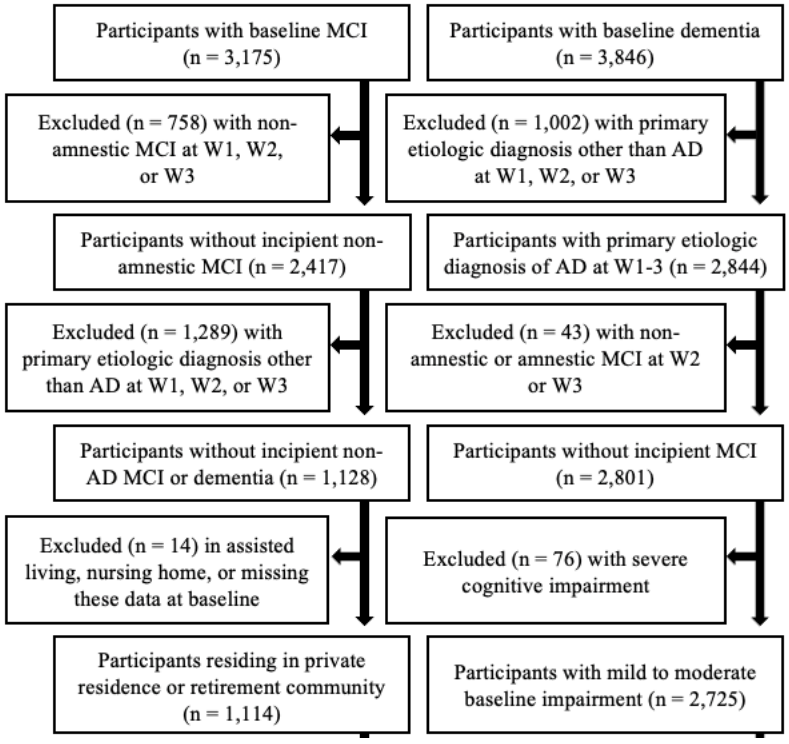
Note. Transition probabilities in bold font correspond to membership in the same latent status at both time points.

Table 3-11. *Odds Ratios for Predictors of Latent Status Membership at Time 1 and 2*

	Time 1 Latent Status	Time 2 Latent Status		
Predictor	Moderately Frail	Severely Frail	Moderately Frail	Mildly Frail
Sex	0.75 [0.61, 0.94] *	0.82 [0.60, 1.12]	0.90 [0.76, 1.08]	1.24 [1.06, 1.45] *
Race/ethnicity	1.17 [0.83, 1.64]	1.10 [0.69, 1.75]	1.15 [0.87, 1.53]	0.95 [0.73, 1.25]
Education	1.00 [0.97,1.03]	0.99 [0.95, 1.03]	1.04 [1.02, 1.07] **	0.99 [0.97, 1.02]
Chronological age	1.08 [1.06, 1.09] ***	1.08 [1.06, 1.10] ***	1.08 [1.07, 1.09] ***	--
Clinical cohort	1.79 [1.32, 2.43] **	2.16 [1.31, 3.56] *	2.22 [1.76, 2.80] ***	1.56 [1.27, 1.88] ***
Global cognition	0.97 [0.94, 1.0] **	0.88 [0.85, 0.91] ***	0.94 [0.92, 0.96] ***	0.99 [0.97, 1.01]
APOE ε4 allele status [a]	0.80 [0.63, 1.01]	1.02 [0.72, 1.44]	--	--

Note. The Not-Clinically Frail status was specified as the reference group at each time point. The dashed lines represent covariate effects that differed significantly across baseline statuses (see results for RG2, step 2) and were thus excluded from these analyses. Odds ratios are presented with 95% confidence intervals. All covariates were entered simultaneously as predictors of latent status membership. Categorical variables were coded as follows: sex (0 = male; 1 = female), race/ethnicity (0 = non-Hispanic White; 1 = Black/African American), clinical cohort (0 = mild cognitive impairment; 1 = Alzheimer's disease), and Apolipoprotein ε4 allelic status (0 = non-carrier; 1 = carrier). [a] Results are based on the final subset of participants who were genotyped (n = 2,649).


Total study sample (N = 42,661)
Excluded (n = 21,349) with ≤ 2 waves of participation
Participants with ≥ 3 waves of data (n = 21,312)
Excluded (n = 1,840) with telephone interviews at W2 or W3
Participants with 3 waves of in person testing (n = 19,472)
Excluded (n = 3,549) with inter-wave intervals > mean days +/- 1SD
Participants with inter-wave intervals within testing +/- 1SD of mean at W2 and W3 (n = 15,923)
Excluded (n = 420) aged < 53 years at baseline
Participants aged ≥ 53 years at baseline (n = 15,503)
Excluded (n = 8,482) diagnosed as cognitively normal at W1 or impaired, not-MCI at W1, W2, or W3


Participants with baseline MCI (n = 3,175)
Participants with baseline dementia (n = 3,846)
Excluded (n = 758) with non-amnestic MCI at W1, W2, or W3
Excluded (n = 1,002) with primary etiologic diagnosis other than AD at W1, W2, or W3
Participants without incipient non-amnestic MCI (n = 2,417)
Participants with primary etiologic diagnosis of AD at W1-3 (n = 2,844)
Excluded (n = 1,289) with primary etiologic diagnosis other than AD at W1, W2, or W3
Excluded (n = 43) with non-amnestic or amnestic MCI at W2 or W3
Participants without incipient non-AD MCI or dementia (n = 1,128)
Participants without incipient MCI (n = 2,801)
Excluded (n = 14) in assisted living, nursing home, or missing these data at baseline
Excluded (n = 76) with severe cognitive impairment
Participants residing in private residence or retirement community (n = 1,114)
Participants with mild to moderate baseline impairment (n = 2,725)

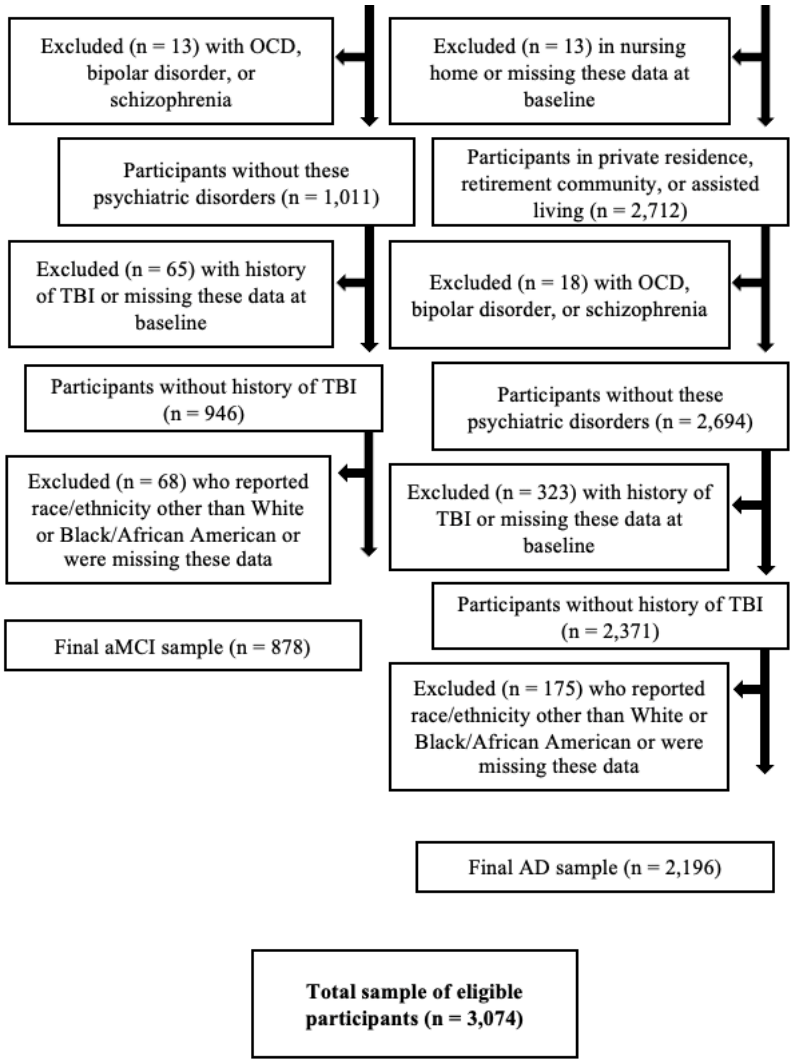


Figure 3-1. Flow diagram of study participants.

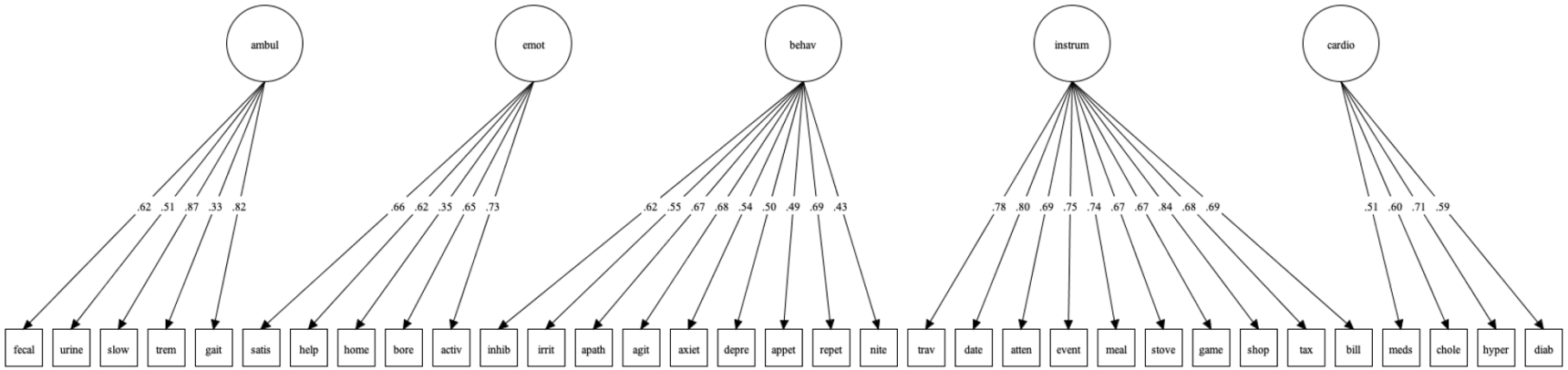


Figure 3-2. Confirmatory factor analysis model conducted with the entire study sample using Time 1 multi-morbidity data.

Note. Ambul, ambulatory ability; Emot, emotional well-being; Behav, behavioral disturbances; Instrum, instrumental health; Cardio, cardiovascular symptoms; Fecal, bowel incontinence; Urine, urinary incontinence; Slow, slowing of motor movements; Trem, tremor; Gait, walking changed; Satis, satisfied with life; Help, feel helpless; Home, prefer to stay home; Bore, often bored; Activ, dropped many activities; Inhib, disinhibition; Irrit, irritability; Apath, apathy; Agit, agitation; Anxiet; anxiety; Depre, depression; Appet; changes in appetite; Repet, repetitive activities; Nite, nighttime behaviors; Trav, difficulty traveling; Date, difficulty remembering appointments; Atten, difficulty paying attention; Event, difficultly tracking current events; Meal, difficulty preparing meal; Stove, difficulty turning off stove; Game, difficulty playing games; Shop, difficulty shopping alone; Tax, difficulty assembling tax records; Bill, difficulty paying bills; Meds, total number of medications; Choles, hypercholesterolemia; Hyper, hypertension; Diab, diabetes. Standardized factor loadings are shown. All loadings were significant at $p < .05$. Latent covariances and residuals are not depicted. Response scales for each item are outlined in Table 3-2.

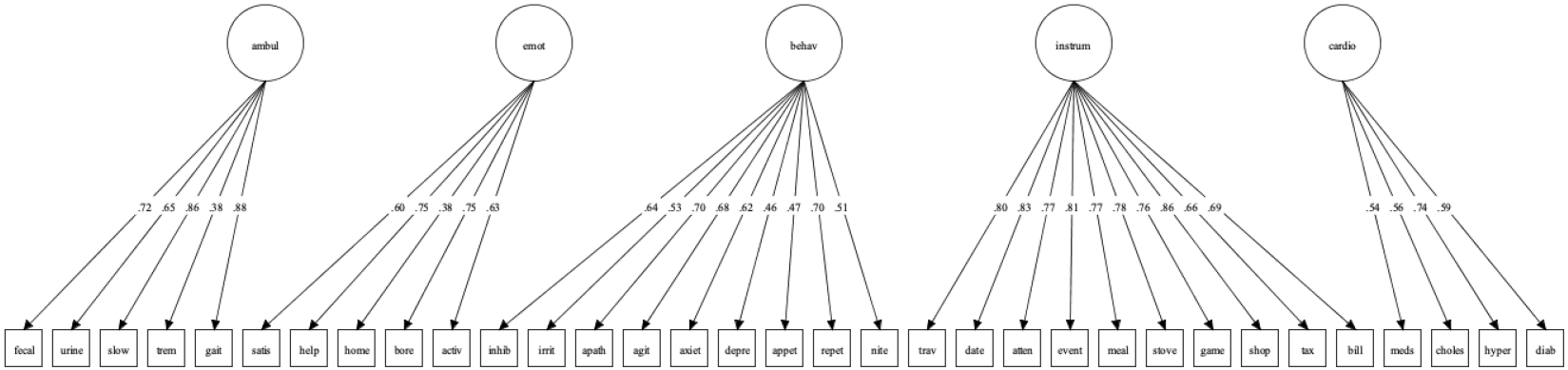


Figure 3-3. Confirmatory factor analysis model conducted with the entire study sample using Time 2 multi-morbidity data.

Note. Ambul, ambulatory ability; Emot, emotional well-being; Behav, behavioral disturbances; Instrum, instrumental health; Cardio, cardiovascular symptoms; Fecal, bowel incontinence; Urine, urinary incontinence; Slow, slowing of motor movements; Trem, tremor; Gait, walking changed; Satis, satisfied with life; Help, feel helpless; Home, prefer to stay home; Bore, often bored; Activ, dropped many activities; Inhib, disinhibition; Irrit, irritability; Apath, apathy; Agit, agitation; Anxiet; anxiety; Depre, depression; Appet; changes in appetite; Repet, repetitive activities; Nite, nighttime behaviors; Trav, difficulty traveling; Date, difficulty remembering appointments; Atten, difficulty paying attention; Event, difficultly tracking current events; Meal, difficulty preparing meal; Stove, difficulty turning off stove; Game, difficulty playing games; Shop, difficulty shopping alone; Tax, difficulty assembling tax records; Bill, difficulty paying bills; Meds, total number of medications; Choles, hypercholesterolemia; Hyper, hypertension; Diab, diabetes. Standardized factor loadings are shown. All loadings were significant at $p < .05$. Latent covariances and residuals are not depicted. Response scales for each item are outlined in Table 3-2.

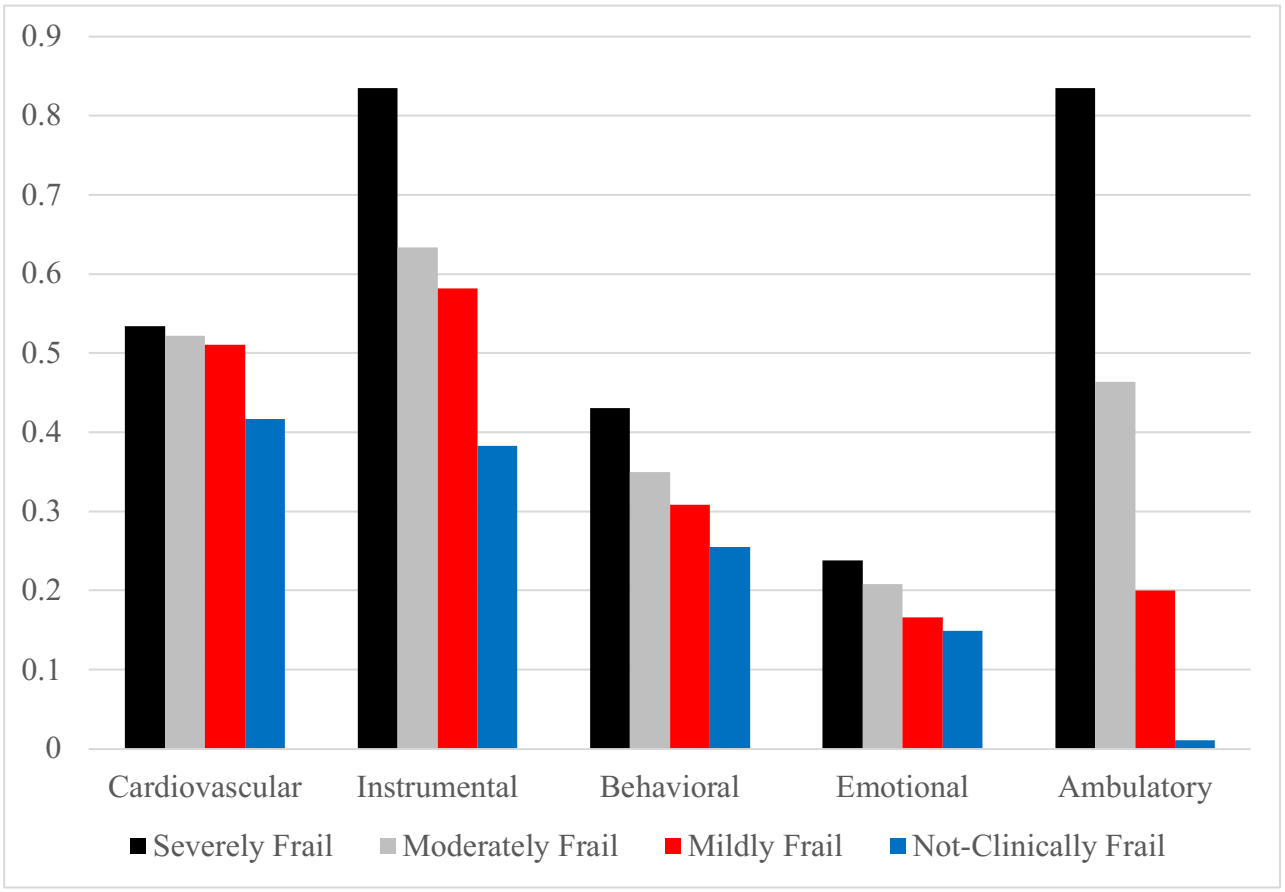


Figure 3-4. Model estimated indicator means for each latent status. Model estimated means for the Not-Clinically Frail and Moderately Frail statuses were constrained to equality over time. Cardiovascular, cardiovascular symptoms; Instrumental, instrumental health; Behavioral, behavioral disturbances; Emotional, emotional well-being; Ambulatory, ambulatory ability.

Chapter 4: Study 3

Application of Machine Learning Technology to the Identification of Frailty-Related Risk Characteristics that Discriminate Four COMPASS-ND Cohorts: Cognitively Normal, Subjective Cognitive Impairment, Mild Cognitive Impairment, and Alzheimer's Disease

Background

Frailty represents a state of increased vulnerability to relatively minor stressors due to impairments in multiple interrelated systems, leading to declining homeostatic reserve and resiliency (Clegg et al., 2013; Morley et al., 2013). Frailty has widespread associations with negative health-related and cognitive aging outcomes (Canevelli et al., 2015; Vermeiren et al., 2016) and has recently been characterized as a cornerstone of geriatric medicine (Walston et al., 2018). Importantly, however, there remains uncertainty about how to best measure and define frailty in clinical-research settings. Since its inception (Fried et al., 2001; Mitnitski et al., 2001), numerous operational definitions and measurement tools have been developed. A recent systematic review revealed that over 65 instruments have been employed (to varying degrees) to identify subgroups of frail older adults and to operationalize risk (Buta et al., 2016). These instruments vary considerably in the number of indicators and domains of aging morbidity they consider. At the same time, it is sobering to note that a subsequent scoping review concluded that the most common operational definition employed in acute care settings was none at all (Theou et al., 2018). It has been suggested that frequent lack of agreement among conceptual models and operationalization techniques may have slowed the development and practical implementation of these tools (Aguayo et al., 2017; Walston et al., 2018). Accumulating literature has thus issued a clarion call for novel approaches to frailty measurement and conceptualization that may (a) lead to wider and more integrative models and (b) produce some resolution of the various empirical and clinical inconsistencies between prevailing frailty research (Anstey & Dixon, 2014; Clegg et al., 2013; Lim et al., 2018; Rockwood & Howlett, 2018).

In the broader area of aging and dementia research, new data-driven approaches have been applied to modeling large-scale and multi-modal indicators of a range of morbidities and

perturbations related to various risk domains that influence brain and cognitive health (Dimitriadis et al., 2018; Hochstetler et al., 2016; McFall et al., 2019; Sapkota et al., 2018). Such analytic approaches have been tested initially in frailty research with cognitively normal (CN) and other aging adults with promising results (Bohn et al., 2021; Peng et al., 2020; Song et al., 2004a; Song et al., 2004b). However, such approaches would ideally be tested across multiple cohorts of older adults, ranging, for example, from asymptomatic groups through impairment and dementia. Accordingly, the present study applied unbiased, machine learning technology to a large database of aging multi-morbidity indicators in order to identify the most important frailty-related features that discriminate pairwise comparisons between CN older controls and the following three clinical cohorts: subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and Alzheimer's disease (AD). This analytical approach allowed us to simultaneously test (in a competitive computational context) a large and representative set of indicators that have primarily been assimilated in a frailty index (Mitnitski et al., 2001) or used to define the physical frailty phenotype (Fried et al., 2001). While hypothesis-guided or composite-related approaches have demonstrated utility for the identification of frailty and prediction of related outcomes (Clegg et al., 2013), these approaches may be limited in identification of important and potentially unexpected modifiable targets for early prevention and intervention efforts. We anticipated that findings would reveal, from a data-driven and cohort specific perspective, central features of frailty that elevate clinical risk for SCI, MCI, and AD.

Despite the significant potential of data-driven (e.g., Bohn et al., 2021; Study 2) and machine learning technologies (Gallucci et al., 2020) to clarify the literature in this area, there are few published applications to date. A handful of studies have employed predictive data mining techniques in order to determine the risk factors (e.g., comorbidities, physical inactivity,

immobility, fluid and neuroimaging biomarkers) that best discriminate non-frail from frail older adults (Hassler et al., 2019; Paul et al., 2020). Importantly, however, results from these studies are predicated on the frailty index (Hassler et al., 2019) or physical frailty phenotype (Paul et al., 2020)— both of which are leading approaches to measuring and conceptualizing frailty. Several studies have opted instead to develop machine learning models that are evaluated for prediction accuracy in classifying surrogates for frailty. For example, Greene and colleagues (2014) used support vector machines to examine the individual and combined utility of three performance-based mobility measures to classify participants according to their level of risk for falling. More recent studies have applied machine learning technologies to large databases of aging multi-morbidity indicators in order to develop predictive models for hospital admissions, permanent entry to care, and/or mortality (Lund et al., 2019; Moldovan et al., 2020; Segal et al., 2017). Perhaps more relevant to the present study, Peng et al. (2020) used random forest (RF) analysis to identify the most important frailty-related indicators that predict unplanned hospitalizations, admissions to an intensive care unit, and mortality. Interestingly, the indicators identified as important predictors in the RF analysis differed markedly from a previous study that used these same data to develop— based on expert recommendation— a multi-morbidity frailty index (Wen et al., 2017). When the latter index was compared against an index derived using RF analysis results, it was reported that the data-driven frailty index had higher prediction accuracy in classifying negative outcomes (Peng et al., 2020).

Importantly, one machine learning study reported that models of frailty may vary as a function of the outcome being considered. Specifically, Tarekegn et al. (2020) applied machine learning techniques to a database of clinical characteristics and socioeconomic factors in order to identify the most important predictors of mortality, urgent hospitalizations, disability, fracture, and

emergency room admissions. Results showed that the predictors deemed to be most important, as well as prediction accuracy, varied across the different outcome variables. To our knowledge, no studies have sought to identify the most important frailty-related features that distinguish clinical cohorts of older adults with SCI, MCI, or AD from a benchmark sample of CN older controls using RF analysis. Notably, we did not explore SCI in our previous study (Bohn et al., 2021) and limited research has examined frailty-SCI associations (Gifford et al., 2019). Individuals with SCI report subjective cognitive complaints but show no signs of objective impairment in measured aspects of cognitive function (Jessen et al., 2014; Stewart, 2012). Because this condition is potentially modifiable (Bhome et al., 2018; Jessen et al., 2014) and accumulating research indicates that it increases risk for exacerbated cognitive decline, impairment, and dementia (Drouin et al., 2020; Fonseca et al., 2015; Koppara et al., 2015; Reisberg et al., 2010), we identify this as a critical area of research attention. Findings from related (non-machine learning) works have shown that frailty is associated with an elevated risk for SCI (Gifford et al., 2019; Hsieh et al., 2018), MCI (Grande et al., 2019; Searle & Rockwood, 2015), and AD (Borges et al., 2019a; Canevelli et al., 2015). Nevertheless, it remains unclear (a) which deficits show the strongest associations with clinical risk for these outcomes and (b) whether prediction patterns vary as a function of the cognitive outcome (or clinical cohort) being considered. The current study fills in these gaps.

Cross-sectional data for this study were drawn from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study, which is the signature clinical cohort study of the Canadian Consortium on Neurodegeneration in Aging. As described in greater detail elsewhere (Chertkow et al., 2019), COMPASS-ND is a pan-Canadian database that includes indicators spanning clinical, neuropsychological, socio-demographic, biological specimen, neuroimaging, and genetic domains. This database was recently used to examine the prevalence of

frailty in a cohort of older adults (n = 150) with a range of neurodegenerative disorders, including SCI (n = 24), MCI (n = 64), and AD (n = 21; Burt et al., 2019). In this study, frailty was operationally defined using the 5-item physical frailty phenotype (Fried et al., 2001) and an 81-item frailty index (Mitnitski et al., 2001). With respect to the former, participants were classified as frail if they endorsed three of the following five characteristics: shrinking, weakness, exhaustion, slowness, and/or low activity (Fried et al., 2001). With respect to the latter, the proportion of deficits accumulated across instrumental or basic activities of daily living (n = 13), quality of life (n = 6), and clinical history (n = 61) was calculated for each participant. These indicators were selected from the COMPASS-ND database using expert recommendation and standard construction guidelines (Searle et al., 2008). Total scores on the frailty index were considered both as (a) a continuous variable, representing the proportion of deficits accumulated (0 = *no deficits endorsed*, 1 = *all deficits endorsed*) and (b) a dichotomous variable, representing whether participants' values exceed a previously established clinical threshold for frailty status (i.e., $\geq$ 0.25; Song et al., 2010). Results indicated that comparable estimates of the prevalence of frailty were generated by each operational definition. Specifically, 14% and 11% of the total study sample were classified as frail according to the physical phenotype and frailty index, respectively (raw agreement = 81%). The average value on the frailty index was 0.15. Important for the present study, the authors noted that there were insufficient data available to examine whether the level or prevalence of frailty varied across subgroups of neurodegenerative disorders and/or was elevated in neurodegenerative disorders as compared to normal cognitive aging.

We contribute to the emerging frailty research in the Canadian Consortium on Neurodegeneration in Aging by (a) considering a wider range of multi-morbidity indicators and (b) employing data-driven quantitative modeling techniques in order to identify the most important

frailty-related features that elevate risk for SCI, MCI, and AD. Specifically, with respect to the first advance, we assembled data for the indicators considered in Burt et al. (2019), as well as data for multi-morbidity indicators and fluid-based biomarkers that were not previously considered. Detecting and validating frailty biomarkers is increasingly recognized as a pressing clinical and research priority (Cardoso et al., 2018; Wallace et al., 2018; Wang et al., 2019). For example, the International Conference on Frailty and Sarcopenia Research Task Force recently concluded that—because current biomarker discovery efforts are largely based on predefined hypotheses— future studies that consider broad panels of potential biomarkers should explore integrated, data-driven bioinformatics approaches (Rodriguez-Mañas et al., 2020). With respect to the second advance, we expand on the findings reported by Burt and colleagues by (a) developing a 30-item data-driven frailty index for each clinical cohort and (b) examining whether frailty levels vary across a spectrum of normal cognitive aging, impairment, and dementia. We selected this number of deficits based on previous research indicating that a frailty index ought to contain a minimum of 30 indicators in order to reliably predict adverse outcomes (Rockwood et al., 2007). Further, we reasoned that, because it is less computationally demanding to calculate a 30-item frailty index and the indicators selected for inclusion are determined using powerful machine learning technology, this reduced index may be more readily integrated into clinical-research settings. Screening for frailty using appropriate criteria is a public health priority. In doing so, clinicians are better positioned to apply interventions that may prevent frailty and benefit cognition, thereby reducing health-care costs and improving quality of life (Burt et al. 2019).

We also planned to advance frailty-related research stemming from the Canadian Consortium on Neurodegeneration in Aging and related databases of aging multi-morbidity by examining whether prediction patterns generalized across sex. Of the related machine learning work

summarized above, only two studies performed prediction analyses as stratified by sex (Greene et al., 2014; Peng et al., 2020), with results suggesting that this is a promising avenue of continued research interest. Further, recent large-scale epidemiological research reported that frailty effects on cognitive level or change trajectories were moderated by sex and concluded that females may experience a wider cognitive deficit from higher frailty levels as compared to males (Thibeau et al., 2019). Nevertheless, because data collection for the COMPASS-ND study was delayed by the pandemic, our study was not sufficiently powered to perform RF analyses as stratified by sex. Specifically, the sex distributions across each of the four cohorts were as follows: CN = 82% female (n = 49); SCI = 83% female (n = 30); MCI = 49% female (n = 57); and AD = 30% female (n = 13). As a result, we decided instead to include sex as a predictor in each of the planned RF analyses. This approach allowed us to test whether the risk for cognitive impairment and dementia varies for males as compared to females. This is a priority area of empirical attention (Andrew & Tierney, 2018; Dubal, 2020; Tierney et al., 2017).

Research Goals

The four specific research goals (RG) of the current study included the sequential application of RF analysis (which can simultaneously process large numbers of individual predictor variables) to a database of 84 multi-morbidity indicators and fluid biomarkers in order to identify the most important frailty-related features that predict membership in the following clinical cohorts: SCI (RG1), MCI (RG2), and AD (RG3). For each of the respective RGs, we tested each targeted clinical cohort against a benchmark sample of CN older controls. This statistical approach accords with previous machine learning research (e.g., McFall et al., 2019; Sapkota et al., 2018) and has the advantage of allowing us to identify both common and distinct domains of deficits that may elevate clinical risk for conversion from normal cognitive aging to aging characterized by cognitive

impairment or dementia. Whereas the first three RGs concerned the clinical cohorts separately, the fourth RG was designed to accomplish an integrative goal and was comprised of several interrelated phases. In the first phase, we constructed a data-driven frailty index for each clinical cohort using data for the top 30 indicators identified in the previous RF analysis. In the second phase, we calculated an 81-item frailty index using the same operational definition as employed in Burt et al. (2019). In the third phase, we tested whether the level of frailty varied across cohorts. In the fourth phase, we tested whether the level of frailty varied complementary conceptualizations of a frailty index.

We expected that findings for RGs 1–3 would reveal important frailty-related features that represent multiple domains or systems of aging morbidity. Further, we anticipated that results for these RGs would reveal clusters of features that generalize across prediction of cognitive impairment and dementia. Specifically, following from the results reported in Studies 1 (Bohn et al., 2021) and 2 of the dissertation research, as well as the accumulating literature on components of the physical frailty phenotype as they relate to SCI, MCI, and AD (Borges et al., 2019a; Borges et al., 2019b; Boyle et al., 2010; Cui et al., 2021; Gifford et al., 2019; Hooghiemstra et al., 2017; McGough et al., 2013), we anticipated that exemplars of mobility and related functional deficits (e.g., timed walk; grip strength) would emerge as salient features across RGs. Consistent with previous work that identified important discriminative features of non-demented cognitive aging trajectories (Caballero et al., 2021; McFall et al., 2019) and adverse frailty-related outcomes (Tarekegn et al., 2020) using RF analysis, we also expected to detect clusters of features that are selectively sensitive to prediction of SCI, MCI, and AD. Descriptive differences have been reported across cohorts of older adults who are CN or have diagnoses of SCI, MCI, or AD in terms of aging multi-morbidity, demographic, and lifestyle characteristics (Hao et al., 2019).

Nevertheless, to our knowledge, this study is the first to identify frailty-related features that elevate clinical risk across the AD spectrum in a competitive machine learning context. With respect to RG4, we anticipated that each successive cohort of older adults with normal cognition, SCI, MCI, or AD would report higher levels of frailty (Hsieh et al., 2018; Kojima et al., 2017; Merchant et al., 2021; Sugimoto et al., 2018). Further, we expected that frailty levels would be comparatively higher for each cohort on the 30-item relative to 81-item index.

Methods

Participants

The COMPASS-ND participants were recruited from 31 data collection sites across Canada. The majority of these were based in academic clinical research settings, including memory clinics, stroke clinics, and movement disorders clinics (Chertkow et al., 2019). Ethics approval was obtained from the Research Ethics Board of each participating centre. Older adults with the following criteria were ineligible to participate in the COMPASS-ND study: (a) presence of significant known chronic brain disease (e.g., moderate to severe chronic static leukoencephalopathy, including previous traumatic injury), multiple sclerosis, a serious developmental handicap, malignant tumors, Huntington's disease, and other rarer brain illnesses; (b) ongoing drug or alcohol abuse; (c) total score < 13 on the Montreal Cognitive Assessment (Nasreddine et al., 2005); (d) symptomatic stroke within the previous year; and (e) unwilling or unable to undergo magnetic resonance imaging scan (Chertkow et al., 2019). Eligible study participants (a) provided written informed consent; (b) were sufficiently proficient in English or French (as indexed by performance on the Language Experience and Proficiency Questionnaire; Marian et al., 2007); (c) lived within one hour of the study site; and (d) had a study partner with whom they interacted on a weekly basis. For the current study, we assembled cross-sectional data

for the following deeply phenotyped cohorts of the COMPASS-ND study: CN (n = 60), SCI (n = 36), MCI (n = 116), and AD (n = 43). By comparison, the Burt et al. (2019) study examined frailty prevalence amongst smaller groups of persons classified as having SCI, MCI, or AD, with no CN older controls available.

Participants' cognitive status was determined by experienced clinicians involved in the COMPASS-ND study using current diagnostic criteria (Chertkow et al., 2019). Participants with subcortical ischemic vascular MCI, dementia of mixed etiology, frontotemporal dementia, Parkinson's disease, and Lewy body dementia were excluded from the current research. Descriptive statistics for the final study sample are presented in Table 4-1 (N = 255; n females = 149; Mage = 71.18, SD = 6.81, age range = 60.05–89.20 years; 92% non-Hispanic White, n = 234).

Measures

Multi-morbidity indicators. We assembled cross-sectional data for aging morbidity indicators that were previously drawn from the COMPASS-ND database in order to operationalize a frailty index (n = 81) or the physical frailty phenotype (n = 2; Burt et al., 2019), as well as data for aging morbidity indicators that were not previously considered (n = 18). Consistent with Studies 1 (Bohn et al., 2021) and 2 of the dissertation research, these indicators spanned multiple domains of aging morbidity, including activities of daily living, sensory functions, mobility, quality of life, emotional well-being, comorbidities, cardiac symptoms, respiratory symptoms and diseases, and physical activity. Procedures for collecting these data included self-report, physical examinations, and formal tests with standardized scales. Each indicator was (re)coded such that scores ranged between 0 (no deficit recorded) and 1 (deficit is maximally expressed; Searle et al., 2008). Where applicable, cut points for continuous indicators were provided in the COMPASS-ND database or determined in accordance with previous empirical research.

Fluid biomarkers. Biosamples of blood, saliva, and urine were collected from COMPASS-ND participants using established operating procedures (Chertkow et al., 2019). We assembled cross-sectional data for 67 fluid biomarkers that (a) have been used to varying degrees in previous frailty-related research and (b) accord with established procedures for assessing frailty using a cumulative frailty index (Searle et al., 2008). Biomarkers were recorded in the COMPASS-ND database as 0 (within established reference range) and 1 (outside established reference range; Blodgett et al., 2017, 2019; Heikkilä et al., 2021; Howlett et al., 2014).

Screening of multi-morbidity indicators and fluid biomarkers. Multi-morbidity indicators and fluid biomarkers were screened for eligibility for inclusion in RF analyses in a series of preliminary analyses. Specifically, we assembled three separate datasets (one for each pairwise comparison) and subsequently removed (a) categorical indicators where < 10% of participants in each cohort were recorded as having the deficit and (b) indicators with a rate of missingness > 50%. The final number of indicators submitted to RF analysis was 64 for SCI, 65 for MCI, and 75 for AD (total *n* across cohorts = 83; see Table 4-2 for a complete reporting of the eligible frailty-related indicators and corresponding response scales). Across the entire study sample, the rate of missingness for the final set of multi-morbidity indicators ranged between 0–3%, with the average rate across predictors at 0.7%. The rate of missingness for the final set of fluid biomarkers ranged between 4–50%, with the average rate across predictors at 18%.

Sex. In line with previous research (e.g., Burt et al., 2019; Thibeau et al., 2019) biological sex was measured in a binary fashion (0 = male, 1 = female) by asking participants to self-report whether they are male or female.

Frailty index calculations. We evaluated the level of frailty using two complementary approaches to calculating a frailty index. First, we constructed a separate 30-item data-driven

frailty index for each clinical cohort using RF analysis results. Specifically, we assembled data for the top 30 predictors identified in RGs 1–3 and subsequently calculated the proportion of deficits that older adults with SCI (i.e., using results from RG1), MCI (i.e., using results from RG2), or AD (i.e., using results from RG3) had accumulated. Values on the data-driven frailty index were calculated for CN controls by taking the average value observed across each of the latter indices. Second, we assembled data for the 81 items used to operationalize a frailty index in Burt et al. (2019) and calculated the proportion of deficits accumulated. The indicators included in the calculation of the 30- and 81-item frailty index are presented in Table 4-3.

Analytical Approach

We used RF analysis (Kuhn & Johnson, 2013) to test the relative predictive importance of frailty-related indicators in discriminating SCI, MCI, or AD from a benchmark sample of CN older adults in a series of three pairwise comparisons. Analyses were performed using Python (3.7.6; www.python.org) and the scikit-learn package (*RandomForestClassifier;* Pedregosa et al., 2011). RF analysis is a recursive partitioning method that combines predictions across multiple classification and regression trees, each of which is based on a random subset of participants and predictors. We note several advantages to this approach. First, it has demonstrated utility for exploring complex, high dimensional datasets related to frailty (Hassler et al., 2019; Kang et al., 2019; Kruse et al., 2018; Peng et al., 2020; Segal et al., 2017; Tarekegn et al., 2020) and prediction of adverse cognitive aging outcomes (Caballero et al., 2020; McDermott et al., 2017; McFall et al., 2019; O'Bryant et al., 2011). Second, it can examine many predictors simultaneously and returns a model with high prediction accuracy— even in studies with small and/or imbalanced (uneven) subsamples. Third, descriptive variable importance measures that reflect the impact of each

variable on the outcome of interest can be extracted (Lundberg et al., 2018; Lundberg & Lee, 2017).

RF models were evaluated using stratified *k*-fold cross-validation. We selected this approach based on literature indicating that stratified *k*-fold cross-validation is recommended for use in instances where the subsamples comprising the pairwise comparison are small and/or imbalanced (Hastie et al., 2009). Stratified *k*-fold cross-validation ensures that each *k*-fold (or subsample) contains roughly the same proportion of each cohort as is represented in the overall sample. In the present study, we used stratified 5-fold cross-validation to divide each pairwise dataset into five equally sized folds (or subsamples). In this approach, four of the five folds were used for training and the remaining fold was used for testing (Wong, 2015). This process was repeated five times, until each fold had been used for testing exactly once. The model then returned the following evaluation metrics, each of which were averaged across the five cross-validation folds. The first metric was the area under the receiver operating characteristic curve (AUC), which is a summary measure of the model's ability to distinguish between CN controls and the target clinical cohort. AUC is interpreted such that 0.5 represents chance, 0.5–0.69 represents poor discrimination, 0.7–0.79 represents acceptable discrimination, 0.8–0.89 represents excellent discrimination, and $\geq$ 0.9 represents outstanding discrimination (Rice & Harris, 2005). The second metric was accuracy, which refers to the total percentage of participants who were correctly classified as either CN or as belonging to the target clinical cohort (i.e., the fraction of true positives and true negatives over all model classifications). The third metric was precision, which represents the percentage of participants who were correctly classified into the target clinical cohort (calculated as true positives / (true positives + false positives)). The fourth metric was recall (or sensitivity), which reflects the percentage of participants from the target clinical cohort who were correctly classified as such

(calculated as true positives / (true positives + false negatives)). The fifth metric was F_1 score, which is an overall measure of the model's accuracy that represents the harmonic mean of precision and recall (calculated as 2 x (precision × sensitivity) / (precision + sensitivity)). Values for the latter four metrics range between 0–1, where higher scores denote better classification accuracy. In studies with imbalanced subsamples— as is largely the case in the present study— AUC and F_1 score are the most robust indicators of classification accuracy (Gómez-Ramírez et al., 2020). As such, we report the five evaluation metrics outlined above for each RF classification model but rely on the latter two metrics when evaluating and interpreting (or assigning a qualitative label) to model fit.

Missing data were handled using *IterativeImputer,* which represents a sophisticated data imputation approach that estimates (or predicts) missing values as a function of all the other predictors in the model (Pedregosa et al., 2011). This process is iterative, meaning that refined missing data estimates are used as input in subsequent iterations of the imputation process. The default estimator in this approach is *BayesianRidge,* which imputes missing data using regularized linear regression. Predictors with the smallest proportion of missing data are estimated first, followed in order by predictors with successively higher proportions of missing data. These analyses were performed using the *sklearn pipeline*. This allowed us to impute missing data (separately) within each cross-validation fold, thereby avoiding data leakage issues (i.e., between training and testing cross-validation folds; Pedregosa et al., 2011). The *sklearn pipeline* involved the following two steps which were conducted sequentially at each fold. First, missing data were imputed. Second, classification analyses were performed using RF analysis (n_estimators=1000, max_depth=3; max_features= auto).

RF analysis results were interpreted using Shapley Additive exPlanation values (SHAP; (Bloch & Friedrich, 2021; Ghorbani & Zou, 2019). These values provide researchers with a unified framework for determining the relative importance (or model contribution) of the considered predictors (Lundberg & Lee, 2017). Previous work indicates that, relative to other individual feature attribution methods, SHAP values are the most robust analytical tool for (a) determining the relative magnitude of each predictor's effect on model classifications while at the same time controlling for overfitting in heterogeneous or small samples (Bloch & Friedrich, 2021) and (b) converging on a single unique solution that balances local accuracy, missingness, and consistency (Lundberg et al., 2020). Further, SHAP values elucidate the direction and magnitude of each predictor's effect.

In the current study, we report two SHAP plots for each RG. These plots provide visual interpretation of RF analysis results (Lundberg et al., 2018). First, we present a global feature importance plot (hereafter referred to as a waterfall plot; see Figure 4-1 for example). This figure depicts the individual and cumulative ratio of the predictors' contribution to the final classification model (represented by the bars and curved line, respectively). Features are presented in descending order of global importance. Second, we present a summary plot (see Figure 4-2 for example). This figure is interpreted such that (a) each dot represents an individual study participant; (b) the color of the dot represents the participant's value on the associated predictor (red dot = high feature value; blue dot = low feature value); and (c) the location of the colored dots along the x-axis indicates the direction and magnitude of each predictor's effect on the model output. Specifically, a high density of red dots to the right side of the vertical line on the x-axis indicates that high feature values predict an increased risk for belonging to the target clinical cohort. Conversely, a high density of blue dots to the right side of the vertical line on the x-axis indicates that low feature

values predict an increased risk of belonging to the target clinical cohort. Dots may (a) pile up to show density (or frequency of each feature value in the dataset); (b) have a skewed distribution (or long tail), which reflects the magnitude of each predictor's effect (increasingly skewed distributions denote larger effects); and/or (c) cluster around 0, which indicates that the predictor is unimportant (or contributes very little to the model; Gómez-Ramírez et al., 2020; Lundberg et al., 2018, 2020). Both the waterfall and summary plot depict the predictors in descending order of global importance, and as such, the rank ordering of frailty-related features remains stable across the figures. Nevertheless, as described above, each figure presents important and complementary information that is useful for model interpretation.

In the current study, we display results for the top 30 predictors identified in each RF classification model. As noted above, data for these predictors were subsequently used to calculate a separate 30-item data-driven frailty index for each clinical cohort. We examined whether values on the 30- and 81-item frailty index varied across cohorts using a one-way analysis of variance (ANOVA) with post-hoc Tukey tests to correct for multiple comparisons. We subsequently tested whether, for each cohort, frailty index values varied across the 30- and 81-item index using paired-sample *t*-tests. For descriptive purposes, we report the proportion of participants who were classified as frail on the 30- and 81-item index using a previously established cut-off value of $\geq$ 0.25 (Burt et al., 2019; Song et al., 2010). These analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY). The criterion for statistical significance was established as $p < .05$.

Results

RG1: RF analysis discriminating SCI from CN controls

We tested 64 predictors in a RF classification model to identify important frailty-related features that discriminate a clinical cohort of older adults with SCI from a benchmark cohort of CN

controls. Findings revealed that overall fit (or performance) of this model was very good (see Table 4-4 for evaluation metrics). Specifically, AUC was 0.89 (represents excellent discrimination) and F_1 score was 0.72 (represents model accuracy based on the harmonic mean of precision and recall). Taken together, these metrics indicate that the RF classification model reliably discriminated these neighbouring cohorts along the AD spectrum. The waterfall plot for the top 30 predictors is presented in Figure 4-1. We interpret results for the top three predictors depicted in this model because (a) there is an evident elbow (or break in the distribution) in the cumulative ratio at this cut-off, (b) these three predictors collectively explained approximately half of the model, and (c) predictors below this cut-off had comparatively smaller contributions to the classification model.

The three features with the highest global importance (as indexed by the composition ratio along the top of the x-axis) are quality of life (memory; explained 21% of the model), lymphocytes (explained 15% of the model), and neutrophils (explained 10% of the model). These features collectively explained 46% of the classification model (as indexed by the cumulative ratio, which is depicted by the blue line). The summary plot is presented in Figure 4-2. These results represent the direction, magnitude, and prevalence of effects associated with the top 30 predictors. The pattern of SHAP values observed for quality of life (memory)— specifically, red dots clustered to the right side of the vertical line on the x-axis— indicates that poorer ratings (represented by higher values) predict an increased risk for SCI. Similarly, lymphocyte and neutrophil counts that fall outside of the normal range (represented by values of 1) predict an increased risk for SCI (as depicted by the high density of red dots clustered to the right side of the vertical line on the x-axis). Each of these effects were relatively large in magnitude (reflected by the far-right location and wide spread of red dots along the x-axis).

RG2: RF analysis discriminating MCI from CN controls

We tested 65 predictors in order to identify important features that distinguish older adults with MCI from CN controls. Results indicated that these cohorts were reliably discriminated by the RF classification model (AUC = 0.88, suggesting excellent discrimination; F_1 score = 0.84; see Table 4-4 for a complete reporting of the evaluation metrics). The waterfall plot for the top 30 predictors is presented in Figure 4-3. We interpret results for the top five predictors depicted in this model because (a) there is an evident elbow in the cumulative ratio at this cut-off, (b) these three predictors collectively explained approximately half of the model, and (c) predictors below this cut-off contributed less to the classification model. The five features with the highest global importance are quality of life (memory, explained 25% of the model), sex (explained 9% of the model), lymphocytes (explained 8% of the model), self-rated eyesight (explained 5% of the model), and quality of life (leisure, explained 4% of the model). Collectively, these predictors explained 51% of the model. The summary plot for the top 30 features is presented in Figure 4-4. Visual inspection of this figure revealed that poorer quality of life (memory, leisure), male sex, abnormal lymphocyte counts, and poorer self-rated eyesight predict an increased risk for MCI. Effects produced by the top three predictors were relatively large in magnitude, whereas effects produced by the fourth and fifth predictors were comparatively smaller in magnitude.

RG3: RF analysis discriminating AD from CN controls

We tested 75 predictors in order to determine important frailty-related features that distinguish older adults with AD from CN controls. Model evaluation metrics indicated that the RF classification model discriminated these two cohorts very well (AUC = 0.98, suggests outstanding discrimination; F_1 score = 0.84; see Table 4-4 for a complete reporting of the results). We present the waterfall plot for the top 30 predictors in Figure 4-5. We interpret results for the top 10 predictors because (a) there is an elbow in the cumulative ratio below this cut-off, (b) these

predictors collectively explained over half of the model, and (c) predictors below this cut-off contributed comparatively less to the classification model. The 10 predictors with the highest global importance include quality of life (memory; explained 15% of the model), olfaction (explained 11% of the model), sex (explained 9% of the model), ability to go shopping (explained 7% of the model), ability to handle money (explained 7% of the model), ability to take medication (explained 5% of the model), visual contrast sensitivity (explained 5% of the model), ability to get to places beyond walking distance (explained 4% of the model), ability to prepare own meals (explained 4% of the model), and ability to do housework (explained 3% of the model). Taken together, these predictors explained 70% of the classification model. The direction and magnitude of the top 30 predictors' effects are presented in Figure 4-6. As highlighted in the figure, poorer quality of life (memory), olfactory deficits, male sex, higher levels of dependence in instrumental activities of daily living (ability to go shopping, handle money, take medication, get to places beyond walking distance, prepare own meals, and do housework), and poorer visual contrast sensitivity exacerbate AD risk. Each of these features produced effects of a relatively large magnitude.

RG4: Examination of frailty across cohorts and indices

We present a list of the indicators included in the calculation of the 30- and 81-item frailty index (Burt et al., 2019) in Table 4-3. This table provides meaningful insight into the extent to which frailty-related features generalize across (a) clinical cohorts and (b) complementary conceptualizations of a frailty index. We report descriptive statistics for the 30- and 81-item frailty index in Table 4-1. Results from a one-way ANOVA revealed that, while values on the 30-item frailty index did not vary across SCI (M = 0.26, SD = 0.09), MCI (M = 0.26, SD = 0.09) or AD (M = 0.28, SD = 0.10), each of these clinical cohorts reported higher levels of frailty as compared to

CN controls (M = 0.17, SD = 0.07; $F(3, 251) = 20.14$, $p < .001$). Similarly, findings for the 81-item index revealed that the level of frailty was comparable across SCI (M = 0.18, SD = 0.07), MCI (M = 0.20, SD = 0.09), and AD (M = 0.21, SD = 0.09). However, only older adults with AD reported higher levels of frailty as compared to CN controls (M = 0.17, SD = 0.07; $F(3, 251) = 2.93$, p = .03). As predicted, values on the 30-item frailty index were higher than the 81-item index for older adults with SCI ($t(35) = 5.43$; $p < .001$), MCI ($t(115) = 11.49$; $p < .001$), or AD ($t(42) = 7.14$; $p < .001$). The level of frailty did not vary across indices for CN controls ($t(59) = 1.04$; $p = .30$).

Convergent with the foregoing results, a comparable proportion of participants with SCI (58.3%), MCI (62.1%), or AD (62.8%) were classified as frail using the 30-item index, however, the prevalence of frailty was higher for each of the respective cohorts as compared to CN controls (8.3%; $\chi^2(3) = 52.16$, $p < .001$). The following proportion of participants were classified as frail using the 81-item index: 13.3% for CN, 16.7% for SCI, 25.9% for MCI, and 34.9% for AD; only older adults with AD differed significantly from CN controls ($\chi^2(3) = 7.91$, $p = .05$). We tested and confirmed that a higher proportion of participants with SCI, MCI, or AD were classified as frail using the 30- as compared to the 81-item index (p-values for all McNemar's tests < .01). The proportion of CN controls classified as frail did not vary across indices (McNemar's test, $p = .45$)

Discussion

This study aimed to resolve selected empirical and clinical inconsistencies between prevailing frailty models through a complementary conceptualization and the application of a data-driven approach to measurement, analyses, and interpretation. Previous research conducted with CN and other aging adults has generated promising results by applying such analytical techniques to heterogeneous databases of aging morbidity indicators (Bohn et al., 2021; Peng et al., 2020; Song et al., 2004a; Song et al., 2004b). We advance this prior work by assembling cross-sectional

multi-morbidity and biomarker data for cohorts of older adults who spanned the AD spectrum. Our specific RGs included identification of the most important frailty-related features that discriminated clinical cohorts of older adults with SCI (RG1), MCI (RG2), or AD (RG3) from a benchmark sample of CN older controls using machine learning-based RF classification analysis. For RG4, we calculated a 30-item data-driven frailty index and an 81-item frailty index (Burt et al., 2019) and tested whether frailty levels varied across cohorts and indices. Results for RGs 1–3 indicated that each classification model reliably discriminated the target clinical cohort from CN controls. Moreover, for each analysis, the following domains of deficits were identified as leading risk characteristics: quality of life (as indicated by results for SCI, MCI, and AD), inflammatory markers (as indicated by results for SCI and MCI), demographic characteristics (as indicated by results for MCI and AD), sensory functions (as indicated by results for MCI and AD), and instrumental activities of daily living (as indicated by results for AD). Importantly, we also identified frailty-related features that (a) did not elevate clinical risk for cognitive impairment or dementia (e.g., depression and polypharmacy) or (b) were selectively sensitive to prediction of SCI (e.g., self-reported balance, falls in the past year, white blood cell count), MCI (e.g., pulse pressure, episodes of fainting, type II diabetes), and AD (e.g., sleep apnea, heart attack, red cell distribution width; see Table 4-3 for generalizability of the top 30 features). Findings for RG4 indicated that, while the level of frailty did not vary across clinical cohorts, older adults with SCI, MCI, or AD reported a higher frailty burden on the 30-item index as compared to (a) CN controls and (b) the 81-item index. Each of the respective findings are discussed in further detail below.

RG1: RF analysis discriminating SCI from CN controls

The RF classification model distinguished older adults with SCI from CN controls with a high degree of accuracy (AUC = 0.89; F_1 score = 0.72), which is particularly notable given that

these are neighbouring cohorts along the AD spectrum. These results contribute to and extend the emerging literature on frailty-SCI associations (Ruan et al., 2020) and identify frailty an important risk factor for SCI. A recent cross-sectional study reported a positive association between the physical frailty phenotype and measures pertaining to SCI such that each additional deficit predicted a nearly threefold increase in the odds of impairment (Gifford et al., 2019). Subsequent epidemiological research examined cross-sectional frailty-SCI associations (Margioti et al., 2020). In this study, frailty was operationalized using the 5-item physical frailty phenotype (Fried et al., 2001), a 61-item frailty index, and a 13-item version of the Tilburg Frailty Indicator (Gobbens et al., 2010). Briefly, the Tilburg Frailty Indicator is a self-report screening questionnaire that incorporates deficits spanning physical, psychological, and social domains. Results indicated that frailty, as defined by each measurement approach, was positively related to risk for SCI. Importantly, however, frailty-SCI associations were comparatively stronger when a multi-domain deficit accumulation approach (as opposed to a physical frailty phenotype) was employed as the operational definition. Convergent results were obtained in the present study, in that the top 30 features identified in machine learning analyses spanned multiple domains or systems of aging morbidity. Specifically, we found that poorer quality of life (memory), abnormal lymphocyte counts, and abnormal neutrophil counts were leading discriminative features. Collectively, these three features explained approximately half of the model's prediction of SCI.

Quality of life represents a broad summary measure of one's perception of their position in life relative to beliefs, goals, concerns, and expectations (Hill et al., 2017; WHOQOL Group, 1998). Quality of life indicators are often (although not always) considered in multi-domain approaches to frailty measurement and conceptualization (Buta et al., 2016; Panza et al., 2018; Sathyan et al., 2019; Searle et al., 2008). Importantly, however, this study is the first to our

knowledge to extract quality of life, particularly as it relates to memory (see Table 4-2 for specific item), from a large and heterogeneous multi-morbidity inventory and identify it as a central risk-elevating characteristic. We note that, while there is some conceptual overlap between this indicator and the clinical criteria for SCI (Chertkow et al., 2019), this specific variable is not included in the diagnostic criteria for SCI in the COMPASS-ND database. Previous research also indicates that quality of life and subjective cognitive complaints are associated (Hill et al., 2017), suggesting that this is as an important area of continued research attention.

Accumulating literature has reported that indicators of peripheral systemic inflammation may represent promising biomarkers of frailty (Collerton et al., 2012; Rodriguez-Mañas et al., 2020; Wang et al., 2019) and have advocated for including such deficits in the operational definition of frailty (Blodgett et al., 2017; Howlett et al., 2014; Mitnitski et al., 2015; Rockwood et al., 2015). For example, Mitnitski et al. calculated a frailty index using cross-sectional data for 40 biomarkers representing inflammation, cellular aging, haematology, and immunosenescence. The authors validated the biomarker-based frailty index against prediction of 7-year mortality and compared its performance against prevailing approaches to frailty measurement and conceptualization. Results indicated that the biomarker-based frailty index predicted mortality; tended to outperform the physical frailty phenotype; performed similarly to a frailty index derived using only clinical conditions; and had the highest prediction accuracy when combined with the latter index. Approximately half of the biomarkers used to compose the biomarker-based frailty index independently predicted mortality, including the following three inflammatory markers that we identified as amongst the top 30 risk characteristics for SCI: abnormal lymphocytes, abnormal neutrophils, and abnormal white blood cell counts (ranked 4th). The authors concluded that findings from this line of research may elucidate the pathophysiologic mechanisms of frailty and thereby

encouraged future studies to extend these results across prediction of additional adverse frailty-related outcomes. The current study fills this gap and addresses an important limitation noted in previous frailty-SCI research. Specifically, Margioti et al. (2020) stated that, due to unavailability, they did not include laboratory tests in their examination of frailty-SCI associations (e.g., routine blood exams representing systemic inflammation, vascular pathology, and stress) and highlighted the need for further studies to address this research aim.

At least two other studies have applied machine learning techniques to inflammatory biomarkers, clinical history, nutritional status, demographic, and lifestyle characteristics in order to identify frailty-related features that exacerbate risk for negative outcomes (Rankin et al., 2020; Subudhi et al., 2021). Importantly, the pattern of results reported converge with the present study. Specifically, Subudhi and colleagues reported that abnormal lymphocyte and neutrophil counts were amongst the top 10 features that increased risk for admission to an intensive care unit (ranked 6th and 4th, respectively) and mortality (ranked 2nd and 3rd, respectively). Rankin and colleagues found that glycated hemoglobin (HbA1c; a blood-based glycemic biomarker and indicator of peripheral systemic inflammation) was amongst the top 20 features that discriminated older adults with cognitive dysfunction from older adults with normal cognition. We also found that abnormal HbA1c was amongst the top 30 features that discriminated older adults with SCI, MCI, or AD from a benchmark sample of CN controls (ranked 7th, 7th, and 22nd, respectively). Taken together, these results advance previous studies implicating chronic inflammation in the clinical etiology of frailty (Fernández-Garrido et al., 2014; Hyde et al., 2019) and lend credence to the notion that inflammation represents a potential explanatory mechanism underlying frailty-cognition associations (Halil et al., 2015; Robertson et al., 2013; Tay et al., 2016). Future machine learning analyses should be applied to the full COMPASS-ND biosample database in order to determine the

relative importance of a wider range of blood-based biomarkers in (a) the operational definition of frailty and (b) determining risk for adverse frailty-related outcomes.

RG2: RF analysis discriminating MCI from CN controls

The RF classification model had high prediction accuracy in discriminating older adults with MCI from CN controls (AUC = 088; F_1 score = 0.84). These findings mark an important contribution to the growing literature on frailty as a potential risk factor for MCI (Borges et al., 2019b; Canevelli et al., 2015; Fabrício et al., 2020; Panza et al., 2018; Robertson et al., 2013). For example, longitudinal data from the Rush Memory & Aging Project showed that physical frailty increased the likelihood of incident MCI, such that each additional deficit predicted a 63% increase in the risk of cognitive impairment (Boyle et al., 2010). Higher levels of physical frailty were also associated with a steeper rate of decline in global cognition, memory performance, perceptual speed, and visuospatial abilities. More recent research examined how components from the physical frailty phenotype affect cognitive performance and decline (Sternäng et al., 2016; Yassuda et al., 2012), as well as risk for MCI (Nyunt et al., 2017), with results suggesting that slower gait speed and reduced grip strength have the strongest associations with these outcomes (Boyle et al., 2010; McGough et al., 2013). We advance these prior works by applying data-driven, machine learning technology to a large database of multi-morbidity indicators and identifying the follow frailty-related features as leading risk characteristics: poorer quality of life (memory, leisure), male sex, abnormal lymphocyte counts, and poorer self-rated eyesight. These features collectively explained half of the model's prediction of MCI.

Limited literature has examined quality of life as a correlate of MCI or dementia and the findings are equivocal, including null, weak, or strong associations (Banerjee et al., 2009; Landeiro et al., 2020; Woods et al., 2014). The present study clarifies the evidence in this area by

demonstrating that poorer quality of life elevates clinical risk across AD spectrum. Specifically, our results indicated that quality of life (memory, leisure) was amongst the top 30 discriminative features for SCI (ranked 1st and 9th, respectively), MCI (ranked 1st and 5th, respectively), and AD (ranked 1st and 18th, respectively). Analogous findings have been reported in the small number of related machine learning works. For example, Rankin and colleagues (2020) identified memory concerns as amongst one of the top frailty-related features that exacerbated risk for cognitive dysfunction. Another study developed binary classification models using 284 aging morbidity indicators and reported that reduced activity participation and boredom were leading features that discriminated frail and non-frail older adults (Hassler et al., 2019). Similarly, Na (2019) applied machine learning analyses to varied aging morbidity indicators and reported that limited activity participation was a top feature that predicted conversion from normal cognitive aging to MCI. Although these studies did not explicitly measure quality of life, the findings reported converge with the notion that poorer perceptions of quality of life (memory, leisure) may (a) represent a critical component of frailty, (b) elevate clinical risk for adverse cognitive aging outcomes (Rockwood et al., 2020), and (c) increase prediction accuracy of composite frailty index approaches. These possibilities could be tested in subsequent research.

Notably, other machine learning research has reported that, consistent with the present study, male sex is a leading risk characteristic for incident MCI (Na, 2019). These results contribute to and extend previous work suggesting that— because the prevalence and incidence of MCI is higher amongst males as compared to females (Ganguli et al., 2004; Jack et al., 2019; Petersen et al., 2010; Ruan et al., 2020)— males may in fact be more vulnerable to cognitive impairment and dementia (Dubal, 2020). This is an important target for future large-scale, longitudinal epidemiological research. The impetus behind this recommendation is threefold. First, our review

indicated that sex (as a predictor or stratification variable) is seldom considered in machine learning analyses (Greene et al., 2014; Peng et al., 2020). Second, the limited body of pertinent research has reported inconsistent findings with respect to the nature and magnitude of sex-frailty-cognition associations (Bohn et al., 2021; Thibeau et al., 2019). Third, advanced understanding of sex differences in cognitive impairment and dementia risk may reveal novel modifiable targets for precision intervention and treatment protocols (Andrew & Tierney, 2018; Dubal, 2020; Tierney et al., 2017).

Our finding that abnormal lymphocyte counts increased risk for MCI converges with results recorded for SCI (ranked 2nd) and AD (ranked 15th) and advances the emerging literature on the diagnostic and clinical utility of blood-based inflammatory biomarkers (Soria-Comes et al., 2020). For example, one study reported that (a) participants with MCI or AD had lower lymphocyte counts and percentages relative to CN controls and (b) abnormal neutrophil-to-lymphocyte ratios discriminated cohorts with MCI (AUC = 0.60) and AD (AUC = 0.73) from CN controls (Dong et al., 2019). Perhaps of greater relevance to the current study, a recent scoping review examined the evidence on lymphocytes as a potential biomarker of frailty and reported that abnormal counts or percentages are associated with an increased risk for frailty emergence and progression (Navarro-Martínez & Cauli, 2021). The authors concluded that lymphocytes should be incorporated into the operational definition of frailty and our results buttress this claim. Routine monitoring of lymphocytes may allow for earlier and more reliable frailty identification in clinical-research settings, as well as provide prognostic information on the likelihood of frailty progression and response to treatment (Navarro-Martínez & Cauli, 2021).

Previous research has assimilated indicators representing visual function (and related sensory deficits) into a continuous frailty index and demonstrated that higher levels predict MCI (Ma et al.,

2017), AD (Mitnitski et al., 2011), or all-cause dementia (Song et al., 2014). We extend this prior work by identifying self-reported eyesight (see Table 4-2 for item) as a critical component of frailty that increases risk for MCI. This finding dovetails with earlier studies that indicated older adults with visual impairment were at a nearly twofold increased risk for exacerbated cognitive decline relative to older adults without such recorded deficits (Fischer et al., 2016; Lin et al., 2004). Similarly, more recent longitudinal research reported that reduced visual acuity increased the odds of MCI by 30–70% (Smith et al., 2021). Nevertheless, it has been noted that much of the available research on this topic has operationalized visual impairment using objective measures of distance visual acuity (Swenor et al., 2019). Because visual function is a complex process, it has been suggested that multiple and varied indicators ought to be considered in future vision-MCI research. Accordingly, Swenor et al. (2019) examined whether MCI risk varied as a function of deficits recorded in visual acuity, visual contrast sensitivity, and stereo visual acuity. Results indicated that, across indicators, impaired visual function increased the likelihood of MCI. In the current study, we examined objective (i.e., impaired visual contrast sensitivity, clinical history of macular degeneration or cataracts) and subjective (i.e., self-reported eyesight) visual deficits in a competitive computational context and identified the latter as a leading risk characteristic. This result is encouraging, as it suggests that quick and inexpensive markers of visual function may be useful for identifying older adults at risk for adverse frailty-related outcomes, including MCI.

RG3: RF analysis discriminating AD from CN controls

The RF classification model yielded excellent accuracy in discriminating older adults with AD from CN controls (AUC = 0.98; F_1 score = 0.84). These results mark an important contribution to the literature on frailty-dementia associations (Canevelli et al., 2015; Panza et al., 2018; Robertson et al., 2013), where there remains some debate surrounding the nature and magnitude of

these associations, as well as how they may vary as a function of the operational definition of frailty (Borges et al., 2019a). For example, several studies have demonstrated that the physical frailty phenotype predicts vascular dementia, is marginally associated with all-cause dementia, and is unrelated to AD (Avila-Funes et al., 2012; Gray et al., 2013; Solfrizzi et al., 2013). Conversely, research employing a multi-domain deficit accumulation approach has reported that frailty predicts conversion from MCI to AD (Trebbastoni et al., 2017), all-cause dementia (Li et al., 2020), and AD (Wang et al., 2017). In the current study, we found that poorer quality of life (memory), sensory deficits (olfaction and visual contrast sensitivity), male sex, and higher levels of dependence in instrumental activities of daily living (ability to go shopping, handle money, take medication, get to places beyond walking distance, prepare meals, and perform housework) are critical features of frailty that exacerbate AD risk. The varied nature of these domains suggests that (a) older adults with broadly constituted health decline may be more susceptible to AD (Mitnitski et al., 2011, 2013; Mitnitski et al., 2004), (b) multiple systems of aging morbidity should be included in the operational definition of frailty in order to reliably identify at-risk older adults (Stephan et al., 2010), and (c) multi-modal interventions may be required for dementia treatment or prevention (Eggink et al., 2019; Livingston et al., 2017).

As previously noted, sensory deficits are often included in composite frailty index approaches (Burt et al., 2019; Ma et al., 2017; Mitnitski et al., 2011; Mitnitski et al., 2004; Song et al., 2014; St John et al., 2017). For example, Ma et al. considered deafness, cataracts, vision disorder, and hearing impairment in their 67-item frailty index. Burt and colleagues included the following indicators from the COMPASS-ND database in their operational definition of frailty: self-reported eyesight, self-reported hearing, macular degeneration, cataracts, and glaucoma. The present study tested the relative predictive importance of the latter indicators together with the

following sensory deficits: visual contrast sensitivity, hearing handicap, and olfaction (see Table 4-2 for items). To our knowledge, no previous work has considered olfaction as amongst one of the indicators of aging multi-morbidity in a cumulative frailty index. The reasons for this pattern are unclear, given that olfactory deficits possess the characteristics required for inclusion in a traditional frailty index (Searle et al., 2008). For example, cross-sectional and longitudinal data indicate that olfactory deficits increase with age (Lara et al., 2015) and may represent a harbinger of adverse brain and cognitive aging outcomes, including exacerbated cognitive decline, impairment, and dementia (Attems et al., 2015; de Moraes e Silva et al., 2018; Jung et al., 2019; MacDonald et al., 2018; Murphy, 2019; Velayudhan, 2015). Furthermore, recent research reported that older adults with olfactory dysfunction had higher frailty index scores (Bernstein et al., 2021) or were more likely to be classified as physically frail (Laudisio et al., 2019). Our results indicated that (a) olfaction and visual contrast sensitivity were leading features that discriminated AD from CN controls (ranked 2nd and 7th, respectively) and (b) self-rated hearing and macular degeneration were amongst the top 30 discriminative features (ranked 21st and 28th, respectively). Notably, we also identified olfaction as amongst the top 30 features that increased risk for MCI (ranked 11th). Collectively, these results bolster previous research including sensory deficits in the operational definition of frailty and add to the growing literature suggesting that olfaction, visual, and auditory deficits may represent modifiable targets for the prevention of accelerated cognitive decline (MacDonald et al., 2018), impairment (Murphy, 2019), and dementia (Livingston et al., 2017, 2020; Risacher et al., 2013, 2020; Rockwood et al., 2020).

We were initially surprised to find that male sex increased risk for AD given that previous studies have suggested that females may be disproportionately affected in terms of prevalence, severity, and rate of AD progression (Mazure & Swendsen, 2016). However, we note three

potential explanations for this result. First, a recent review reported that, although females often have a greater risk of developing AD as compared to males, these differences are typically restricted to advanced ages (i.e., ≥ 80 years; Dubal, 2020). In the current research, the average age of study participants was well below this threshold (M = 71.18 years). Second, considerable research has established chronological age (per se) as the single most important risk factor for AD (Riedel et al., 2016). Findings from follow-up analyses indicated that males (M = 72.38) were significantly older than females (M = 70.32; $p < .05$). Third, as outlined above, higher levels of frailty increase AD risk. Notably, males (M = 0.27) in our study reported higher values on the 30-item frailty index as compared to females (M = 0.23; $p < .01$), suggesting that sex differences in the burden of frailty may be an important mechanism contributing to the increased AD risk for males. We identify this as an important follow-up question for future COMPASS-ND research.

It is interesting that each of instrumental activities of daily living indicators considered in this RF analysis emerged as salient risk characteristics. Deficits in performing instrumental activities of daily living have been widely assimilated into composite frailty index approaches (e.g., Burt et al., 2019; Searle et al., 2008) and are established risk factors for cognitive impairment and dementia (Cloutier et al., 2021; Mao et al., 2018; Roehr et al., 2019). For example, previous research suggests that a reduced capacity to perform instrumental activities of daily living may appear early in the neuropathological cascade of AD (Amieva et al., 2008; Brown et al., 2011; Cloutier et al., 2021; Jutten et al., 2019; Pérès et al., 2008). Further, individuals presenting with both functional declines and SCI (Roehr et al., 2019) or MCI (Jekel et al., 2015) may be particularly vulnerable for dementia conversion. At least two other studies have concluded that deficits in instrumental activities of daily living are a critical feature of data-driven frailty models (Goonawardene et al., 2018; Hassler et al., 2019). Goonawardene and colleagues applied machine learning techniques to

in-home sensor data (i.e., motion sensors that track participants' movement throughout the home) and reported that kitchen activity levels and kitchen use duration were key characteristics that discriminated frail from non-frail older adults. Hassler et al. applied machine learning analyses to a large number of aging morbidity indicators and found that difficulties in performing housework, using the telephone, shopping, cooking, or public transportation were leading features that differentiated frail and non-frail older adults.

RG4: Examination of frailty across cohorts and indices

As emphasized in the preceding sections, examination of prediction patterns across clinical cohorts revealed clusters of frailty-related features that generalized across prediction of SCI, MCI, and AD. Importantly, however, we also identified clusters of deficits that were either (a) unassociated with clinical risk for SCI, MCI, and AD or (b) selectively sensitive to prediction of these cognitive outcomes (or clinical cohorts). Accordingly, we calculated a separate 30-item data-driven frailty index for each clinical cohort using cross-sectional data for the top 30 features identified in the machine learning analyses. We present the full set of cohort comparisons in Table 4-3 and discuss generalizability of the frailty-related features across RGs 1–3 below, followed by a specific overview of findings for RG4.

As detailed in the foregoing discussion, quality of life (memory, leisure) and inflammatory biomarkers (lymphocytes, HbA1c) emerged as important frailty-related features that elevated clinical risk for SCI, MCI, and AD. We elaborate on these findings here and note that sleep (disturbances, medication), oral health and nutritional factors (self-reported appetite, mouth health, difficulty swallowing), and functional indicators (grip strength) were also identified as amongst the top 30 features that increased risk for these cognitive outcomes. Sleep disturbances have received some empirical interest for their role in the development cognitive impairment and dementia

(Rockwood et al., 2020; Wennberg et al., 2017), with evidence suggesting that deficits in this domain may exacerbate risk. Interestingly, our results indicated that increased usage of sleep medication was associated with a reduced risk for SCI, MCI, and AD. Several viable explanations have been posited to underlie sleep-cognition associations (e.g., sleep may promote repair of damage caused by other factors; Livingston et al., 2017), however the causal direction and pathophysiologic mechanisms of this relationship remains unclear (Wennberg et al., 2019). Oral health (Nangle et al., 2019) and nutritional factors (Artero et al., 2008; Reisberg et al., 2010) have also been identified as potentially modifiable risk factors for exacerbated cognitive decline, impairment, and dementia. Oral health may affect brain and cognitive aging via specific biological mechanisms, such as common inflammatory pathways or reduced nutritional intake (Noble et al., 2013).

Importantly, of the five indicators included in the operational definition of the physical frailty phenotype (Fried et al., 2001), grip strength was the only characteristic that generalized across prediction SCI, MCI, and AD. These results replicate previous studies demonstrating an independent association between grip strength and reduced cognition function (Cui et al., 2021; Sternäng et al., 2016; Zammit et al., 2019) and extend earlier work suggesting that components of the frailty phenotype may be differentially associated with risk for cognitive impairment and dementia (Al Saedi et al., 2019; Boyle et al., 2010; Gifford et al., 2019; Hooghiemstra et al., 2017; Walston et al., 2018). Specifically, our results indicated that unintentional weight loss was selectively sensitive to prediction of SCI (ranked 19th), exhaustion predicted SCI and MCI (i.e., everything an effort; ranked 30th and 13th, respectively), and AD was selectively predicted by slowness and low physical activity (ranked 11th and 30th, respectively). This pattern of results advances the literature on frailty as a risk factor for cognitive impairment and dementia by

suggesting that a multi-domain deficit accumulation approach may be a more robust and reliable indicator of frailty status and risk for adverse cognitive aging outcomes or trajectories as compared to the physical frailty phenotype.

Importantly, we also identified several frailty-related features that did not elevate risk across the AD spectrum (e.g., waist-to-hip ratio, hearing handicap, stroke) and discuss two such predictors here— depression and polypharmacy. Each of these indicators have been included in composite frailty indices (Bohn et al., 2021; Burt et al., 2019; Margioti et al., 2020; Thibeau et al., 2019; Ward et al., 2021a) and have been characterized (to varying degrees) as independent risk factors for cognitive impairment and dementia. For example, several systematic reviews have examined the evidence on depression as it relates to SCI and MCI and concluded that, in general, higher levels of depressive symptomatology exacerbate risk (Cooper et al., 2015; Hill et al., 2016; Mourao et al., 2016). Importantly, however, the authors cautioned that the evidence in this area remains somewhat mixed and noted that future studies are required to establish the reliability of these associations. The current study answers this call by deploying a powerful machine learning prediction technology that evaluates the relative importance of multiple frailty-related risk factors simultaneously. In this competitive analytic context, we observed that depression did not distinguish clinical cohorts of older adults with SCI or MCI from CN controls. The evidence on depression as a potential risk factor for dementia is less mixed (Livingston et al., 2017, 2020). For example, the 2017 *Lancet* Commission report on dementia prevention, intervention, and care concluded that up to a third of dementia cases are attributable to nine modifiable risk factors, including depression. Our results suggest that, when tested against a wide and representative set of aging morbidity indicators using machine learning technologies, depression is not a central characteristic of frailty that elevates AD risk. Similarly, although several studies suggest that

polypharmacy may be associated with reduced cognitive function (Langeard et al., 2016; Rawle et al., 2018), cognitive impairment (Margolis et al., 2021), and dementia (Cheng et al., 2018; Leelakanok & D'Cunha, 2019), polypharmacy did not emerge as a leading feature of frailty that increased risk for SCI, MCI, or AD. Interestingly, a recent scoping review reported that this variable may be more likely to appear in sex stratification analyses. We intend to examine this possibility in a follow-up study.

Notably, our RF classification models revealed frailty-related indicators that were selectively sensitive to prediction of SCI (e.g., self-reported balance, falls in the past year, white blood cell count), MCI (e.g., pulse pressure, episodes of fainting, type II diabetes), and AD (e.g., sleep apnea, heart attack, red cell distribution width). These findings run in parallel to previous machine learning research that reported prediction patterns varied across outcomes, including exacerbated cognitive decline (McFall et al., 2019), disability, hospitalization, and mortality (Tarekegn et al., 2020). Our results have implications for precision health solutions to better identify and target clinically relevant signatures of frailty risk across the AD spectrum. Further, our results suggest that older adults at risk for frailty and negative cognitive aging outcomes can be reliably identified by a relatively small number of data-driven aging morbidity indicators. Specifically, across RF classification models, the top 30 frailty-related features explained approximately 90% of the model's prediction of SCI, MCI, or AD.

Results for RG4 indicated that data-driven frailty index levels did not vary across SCI, MCI, or AD (*M* index score = 0.27) and neither did the prevalence of frailty (*M* prevalence = 62%). However, consistent with our expectations and previous research (Gifford et al., 2019; Kojima et al., 2017; Sugimoto et al., 2018), we found that older adults with SCI, MCI, or AD reported higher levels of frailty on the 30-item index relative to CN controls. When frailty was measured using an

81-item index that was operationalized in previous COMPASS-ND research (Burt et al., 2019), we found that (a) the level and prevalence of frailty did not vary across clinical cohorts (*M* index score = 0.20; *M* prevalence = 26%) and (b) only older adults with AD reported a higher burden and prevalence of frailty relative to CN controls. We subsequently compared the level and prevalence of frailty across the 30-item and 81-item index and found that, across clinical cohorts, the former index generated larger estimates of these outcomes. Future work could examine predictive validity of these complementary conceptualizations of a frailty index (Peng et al., 2020).

Strengths and limitations

We note several methodological strengths. First, data-driven analyses were conducted using powerful machine learning technologies. This analytical approach represents a promising alternative to traditional research methods for identifying the key markers of frailty within a cluster of aging morbidity indicators, as well as improving prediction of adverse frailty-related outcomes and identifying clinically relevant and potentially unexpected signatures of risk. Further, our classification models (a) incorporated a wide and representative set of frailty-related features, (b) were predicated on well-defined surrogates for frailty, (c) demonstrated high prediction accuracy in discriminating clinical cohorts of older adults with SCI, MCI, or AD from a cohort of CN controls, (d) elucidated the domains of deficits (and individual indicators) that increased risk for these outcomes, and (e) interpreted black-box RF classification models using SHAP values (Bloch et al., 2021). The latter consideration has relevance in clinical-research settings, where model interpretation may be of greater significance than overall prediction performance (Lundberg et al., 2020). Although expanding, relatively few studies have leveraged these analytical techniques in order to advance the literature on frailty measurement and conceptualization. Second, cross-sectional data were drawn from the COMPASS-ND database, which represents the most

comprehensive and ambitious Canadian study of neurodegenerative disorders (Chertkow et al., 2019). Participants in this study were deeply phenotyped cohorts of older adults who varied along the spectrum of normal cognitive aging, through to impairment and dementia. By including a cohort of CN older controls, we were able to identify potentially modifiable and unexpected risk characteristics that could be targeted prior to the onset of clinically detectable frailty and cognitive impairment. To our knowledge, no previous works have developed data-driven models of frailty and subsequently validated them against prediction of SCI, MCI, and AD. We encourage future replications and extensions within the COMPASS-ND database, as well as in related large-scale longitudinal studies of brain and cognitive aging.

We acknowledge several potential study limitations. First, the uneven sex distributions coupled with relatively small subsample sizes precluded us from testing whether prediction patterns varied for males as compared to females. We intend to address this research aim in follow-up work. Findings from this line of research have applications to advancing understanding of sex differences in the clinical etiology and progression of frailty, as well as in frailty-cognition associations. Second, due to unavailability, we were unable test a larger and more comprehensive panel of fluid biomarkers in the RF classification models. Future studies could explore whether inclusion of additional biomarkers related to general health, sex-related hormones, inflammation, lipid metabolism, and oxidative stress may result in prediction patterns that diverge from the present research. However, we restricted our sampling of fluid biomarkers to domains that have been previously linked to frailty and aging (Al Saedi et al., 2019; Rodriguez-Mañas et al., 2020). As longitudinal follow-up COMASS-ND data become available, we plan to identify frailty-related characteristics that exacerbate risk for accelerated cognitive decline, conversion of SCI and MCI, and dementia progression.

Conclusions

To summarize, the current study advances the literature on frailty measurement and conceptualization by (a) testing a wide and representative set of aging morbidity indicators from the COMPASS-ND database in a competitive computational context and (b) identifying selected important frailty-related characteristics that elevate clinical risk for SCI, MCI, and/or AD. Using ML analyses, we identified domains of deficits that varied in terms of their contribution to the RF classification model, but nonetheless generalized across prediction of cognitive outcomes (or clinical cohorts), including quality of life (memory, leisure), inflammatory biomarkers (lymphocytes, HbA1c), sleep (disturbances, medication), functional markers (grip strength), oral health and nutritional factors (self-reported appetite, mouth health, difficulty swallowing). This pattern of results suggests that (a) multi-domain deficit accumulation approaches may better capture the typical heterogeneity of frailty as compared to syndromic definitions and (b) composite indices incorporating these domains of deficits may better identify older adults an increased risk for frailty and associated negative outcomes. Notably, we also detected frailty-related features that have been previously assimilated in composite index (e.g., dependence in instrumental activities of daily living, self-reported hearing) or phenotypic approaches (e.g., unintentional weight loss, timed walk) that were selectively sensitive to prediction of SCI, MCI, and AD. As such, we calculated a separate 30-item data-driven frailty index for each clinical cohort. Subgroup analyses indicated that the level and prevalence of frailty did not vary across clinical cohorts but was elevated in comparison to (a) a benchmark sample of CN controls and (b) an 81-item frailty index that was operationalized in previous research using standard guidelines (Searle et al., 2008) and expert recommendation (Burt et al., 2019). To our knowledge, this study is the first to systematically examine these research aims using sophisticated data-driven analyses. Our findings have

application to precision interventions to better identify and target frailty across the AD spectrum (Apóstolo et al., 2018; Robertson et al., 2013).

Table 4-1. *Demographic and Clinical Characteristics Disaggregated by Cohort*

Characteristic	CN (n = 60)	SCI (n = 36)	MCI (n = 116)	AD (n = 43)	sig
n(%) female	49 (82%) [a]	30 (83%) [a]	57 (49%) [b]	13 (30%) [c]	***
Age (years)	69.23 (5.52) [a]	69.62 (6.81) [a]	71.16 (6.48) [a]	75.26 (7.70) [b]	***
Education (years)	15.84 (3.15)	17.49 (3.11)	15.75 (3.89)	15.34 (4.37)	*ns*
n(%) married	37 (62%) [a]	17 (47%) [a]	75 (65%) [a]	35 (81%) [b]	*
n(%) Non-Hispanic White	58 (97%) [a]	34 (94%) [a,b]	100 (86%) [b]	42 (98%) [a]	*
MoCA	27.90 (1.50) [a]	27.81 (1.33) [a]	24.28 (3.08) [b]	18.63 (3.56) [c]	***
30-item frailty index	0.17 (0.07) [a]	0.26 (0.09) [b]	0.28 (0.10) [b]	0.28 (0.10) [b]	***
n(%) frail	5 (8%) [a]	21 (58%) [b]	72 (62%) [b]	27 (63%) [b]	***
81-item frailty index	0.17 (0.07) [a]	0.18 (0.07) [a]	0.20 (0.09) [a]	0.21 (0.09) [b]	*
n(%) frail	8 (14%) [a]	6 (17%) [a,b]	30 (26%) [a,b]	15 (35%) [b]	*

Note. Results are presented as mean (standard deviation) unless noted as otherwise. *p*-values are based on one-way analysis of variance or chi-square tests, as appropriate. We adjusted for multiple comparisons using post-hoc Tukey tests. Abbreviations: CN, cognitively normal; SCI, subjective cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; sig, significance; *ns*, not significant; MoCA, Montreal Cognitive Assessment. [a,b,c] Values with different superscripts significantly differ from one another.

[*] *p*-value < .05 [***] *p*-value < .001

Table 4-2. *Indicators Eligible for Inclusion in Random Forest Analyses*

Category	Multi-Morbidity Item	Coding
IADL	Getting to places beyond walking distance *, ^	0 = without help; 0.5 = with some help; 1 = completely unable
	Going shopping for groceries or clothes *, ^	
	Preparing meals *, ^	
	Doing housework *, ^	
	Taking medication ^	
	Handling money ^	
ADL	Trouble getting to bathroom in time ^	0 = no; 1 = yes
Low activity	Physical activity (PASE score) *, ^	0 = ≥64 for men or ≥52 for women; 1 = <64 for men or <52 for women
Mobility	Self-reported balance	0 = very good; 0.5 = pretty good; 1 = very poor
	Balance confidence (ABC score)	0 = high; 0.5 = moderate; 1 = low
	Timed walk (averaged over three 6m trials) *	> 1m/s = 0; < 1m/s = 1
	Falls in the past year ^	0 = no; 1 = yes
QOL	Physical health *, ^	0 = excellent; 0.33 good; 0.66 = fair; 1 = poor
	Energy *, ^	
	Mood *, ^	
	Memory ^	

	Ability to do chores around the house *, ^	
	Ability to do things for fun *, ^	
Anthropometric measures	Waist-to-hip ratio	≤ 0.85 females, ≤ 0.96 males = 0; > 0.85 females, > 0.96 males = 1
	Waist circumference (cm)	< 88 females, < 102 males = 0; > 88 females, > 102 males = 1
	Body mass index (kg/m^2) *	0 = 18.5-25; 0.5 = 25 to < 30; 1 = < 18.5 or ≥ 30
	Unintentional weight loss *, ^	0 = no; 1 = yes
Sensory	Self-reported eyesight *, ^	0 = excellent; 0.25 = very good; 0.50 = good; 0.75 = fair; 1 = poor or non-existent
	Self-reported hearing *, ^	
	Hearing handicap (HHIE score)	0 = no hearing handicap; 0.5 = mild/moderate handicap; 1 = significant handicap
	Olfaction (B-SIT score)	≥ 11 = 0; ≤ 10 = 1
	Visual contrast sensitivity (Mars Letter Contrast Sensitivity Test)	0 = normal; 0.5 = moderate; 1 = severe impairment
	Cataracts ^	0 = no; 1 = yes

	Macular degeneration ^	
Sleep	Sleep duration (PSQI score)	0 = none; 0.33 = slight problem;
	Sleep efficiency (PSQI score)	0.66 = somewhat a problem; 1 =
	Sleep disturbances (PSQI score)	big problem
	Daytime dysfunction (PSQI score)	
	Sleep latency (PSQI score)	
	Sleep medication (PSQI score)	
	Self-reported sleep quality [*, ^]	0 = very good; 0.33 = fairly good;
		0.66 = fairly bad; 1 = very bad
Clinical assessment	Grip strength (averaged over three trials) [*, ^]	Males: for BMI ≤ 24, GS ≤ 29; for
		BMI 24.1-28, GS ≤ 30; for BMI >
		28, GS ≤ 32
		Women: for BMI ≤ 23, GS ≤ 17;
		for BMI 23.1-26, GS ≤ 17.3; for
		BMI 26.1-29, GS ≤ 18; for BMI >
		29, GS ≤ 21
	Pulse pressure (mmHg) [*]	0 = 32.13-63.90; 0.5 = 64-75.9; 1
		= < 32.12 or 76+
	Resting heart rate (bpm) [*]	0 = 60-99; 1 = < 60 or 100+
	Self-reported current health [b, *, ^]	
	Fatigue- everything an effort [c, ^]	
	Fatigue- could not get going [c, *, ^]	

Self-reported appetite [e, ^]

Coughing, choking, pain when swallowing [f, ^]

Self-reported mouth health [d, ^]

Eating discomfort due to mouth problems [f, ^]

Avoid eating particular food due to mouth [f, ^]

Polypharmacy [h, *, ^]

Osteoarthritis [a, *, ^]

Chronic respiratory condition [a, *, ^]

Shortness of breath [a, *, ^]

Sleep apnea [a, *, ^]

High blood pressure or hypertension [a, *, ^]

Atrial fibrillation or irregular heartbeat [a, *, ^]

Heart attack, congestive heart failure [a, *, ^]

Peripheral vascular disease [a, *, ^]

Mini-stroke or TIA [a, *, ^]

Episodes of fainting [a, ^]

Orthostatic blood pressure drop [a]

Vertigo or dizziness

Type II diabetes [i, *, ^]

High cholesterol [a, *, ^]

Hypothyroidism [a, *, ^]

Osteoporosis [a, *, ^]

Stomach ulcers [a, *, ^]

	Irritable bowel syndrome [a]	
	Chronic constipation [a, ^]	
	Urinary incontinence [a, ^]	
	Cancer [a, *, ^]	
	Major depressive disorder [a, *, ^]	
	Generalized anxiety disorder [a, ^]	
Fluid biomarkers	Hemoglobin	0 = inside established reference
	Hemoglobin A1c	range; 1 = outside established
	Mean corpuscular hemoglobin concentration	reference range
	Mean corpuscular hemoglobin	
	Mean corpuscular volume	
	White blood cell count	
	Red blood cell count	
	Red cell distribution width	
	Number of lymphocytes	
	Number of neutrophils	
	Hematocrit	
Sex	Male or Female	0 = male; 1 = female

Note. Abbreviations: IADL, instrumental activities of daily living; ADL, activities of daily living; QOL, quality of life; PASE, adapted Physical Activity Scale for the Elderly (Washburn et al., 1993); ABC, Activities-specific Balance Confidence Scale (Powell & Myers, 1995); HHIE, Hearing Handicap Inventory for the Elderly— screening version (Ventry & Weinstein, 1982); B-SIT, Brief Smell Identification Test (Menon et al., 2013); PSQI, Pittsburgh Sleep Quality Index (Buysse et al., 1989); TIA, transient ischemic attack. [*]

Denotes indicators that are comparable to those used in Bohn et al. (2021) to calculate a frailty index. ^ Denotes indicators that were employed in Burt et al. (2019) to calculate a frailty index. [a] 0 = no; 1 = yes; [b] 0 = very good; 0.25 = good; 0.50 = average; 0.75 = poor; 1 = very poor; [c] 0 = rarely or none of the time; some or a little of the time; 1 = a moderate amount; most of the time; [d] 0 = excellent; 0.25 = very good; 0.50 = good; 0.75 = fair; 1 = poor or non-existent; [e] 0 = very good; 0.33 = good; 0.66 = fair; 1 = poor; [f] 0 = never; 0.33 = rarely; 0.66 = sometimes; 1 = often or always; [g] 0 = very good; 0.33 = fairly good; 0.66 = fairly bad; 1 = very bad; [h] 0 = 0-4 medications; 0.5 = 5-7 medications; 1 = 8+ medications. [i] 0 = no; 0.5 = borderline/high blood sugar; 1 = type I or II diabetes.

Table 4-3. *Generalizability of the Top 30 Features Identified in Random Forest Analyses*

Indicators Submitted to RF Analysis	SCI	MCI	AD	Burt et al.
Getting to places beyond walking distance (IADL)	^	^	X	X
Going shopping for groceries or clothes (IADL)	^	^	X	X
Preparing own meals (IADL)	^	^	X	X
Doing housework (IADL)	X	^	X	X
Taking own medication (IADL)	^	^	X	X
Handling own money (IADL)	^	^	X	X
Trouble getting to bathroom in time (ADL)	X			X
Physical activity			X	X
Self-reported balance	X			
Balance confidence	X	X		
Timed walk			X	X
Falls in the past year	X			X
Physical health QOL	X	X		X
Energy QOL	X	X		X
Mood QOL		X	X	X
Memory QOL	X	X	X	X
Ability to do chores around the house QOL				X
Ability to do things for fun QOL	X	X	X	X
Waist-to-hip ratio				
Waist circumference	X			
Body mass index	X			
Unintentional weight loss	X	^		X
Self-reported eyesight		X		X
Self-reported hearing			X	X
Hearing handicap				
Olfaction		X	X	
Contrast sensitivity	^		X	
Cataracts				X

Macular degeneration	^	^	X	X
Sleep duration (PSQI score)		X	X	
Sleep efficiency (PSQI score)		X		
Sleep disturbances (PSQI score)	X	X	X	
Daytime dysfunction (PSQI score)	X			
Sleep latency (PSQI score)		X	X	
Sleep medication (PSQI score)	X	X	X	
Self-reported sleep quality				X
Grip strength	X	X	X	X
Pulse pressure		X		
Resting heart rate	X			
Fatigue- everything an effort	X	X		X
Fatigue- could not get going		X		X
Self-reported current health		X		X
Self-reported appetite	X	X	X	X
Coughing, choking, pain when swallowing	X	X	X	X
Self-reported mouth health	X	X	X	X
Eating discomfort due to mouth problems	X			X
Avoid eating particular food due to mouth				X
Polypharmacy				X
Osteoarthritis				X
Chronic respiratory condition				X
Sleep apnea			X	X
High blood pressure or hypertension	X	X		X
Hyperlipidemia		X	X	X
Atrial fibrillation or irregular heartbeat				X
Heart attack, congestive heart failure	^	^	X	X
Peripheral vascular disease		^	^	X
Mini-stroke or TIA	^		^	X
Episodes of fainting		X		X
Orthostatic blood pressure drop	X	X		

Vertigo or dizziness		X		
Type II diabetes	^	X		X
Hypothyroidism	X			X
Osteoporosis				X
Stomach ulcers				X
Irritable bowel syndrome		^	^	
Chronic constipation	^		^	X
Urinary incontinence				X
Cancer				X
Major depressive disorder				X
Generalized anxiety disorder	X			X
Sex		X	X	
Hemoglobin	^			
Hemoglobin A1c	X	X	X	
Mean corpuscular hemoglobin concentration	^	^		
Mean corpuscular hemoglobin	^	^		
Mean corpuscular volume	^		^	
White blood cell count	X	^	^	
Red blood cell count				
Red cell distribution width	^	^	X	
Number of lymphocytes	X	X	X	
Number of neutrophils	X	^	^	
Hematocrit	^			
Dressing and undressing (ADL)	^	^	^	X
Eating (ADL)	^	^	^	X
Taking care of appearance (ADL)	^	^	^	X
Walking (ADL)	^	^	^	X
Getting in/out of bed (ADL)	^	^	^	X
Using the telephone (ADL)	^	^	^	X
Rheumatoid arthritis	^	^	^	X
Other arthritis	^	^	^	X

Hematologic disease	^	^	^	X
Hyperthyroidism	^	^	^	X
Angina or chest pain	^	^	^	X
Inflammatory bowel disease	^	^	^	X
Celiac disease	^	^	^	X
Glaucoma	^	^	^	X
Psoriasis	^	^	^	X
Kidney disease	^	^	^	X
Liver disease	^	^	^	X
Hepatitis	^	^	^	X
HIV	^	^	^	X
Bipolar disorder	^	^	^	X
Other mood disorder	^	^	^	X
Phobic disorder	^	^	^	X
Obsessive compulsive disorder	^	^	^	X
Panic disorder	^	^	^	X
Post-traumatic stress disorder	^	^	^	X
Schizophrenia	^	^	^	X
Suicide attempt	^	^	^	X
Hip replacement	^	^	^	X
Knee replacement	^	^	^	X

Note. ^ Denotes indicators that were excluded from the associated pairwise comparison (for reasons as noted in the Methods section). RF, random forest; SCI, subjective cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; IADL, instrumental activities of daily living; ADL, activities of daily living; QOL, quality of life; PSQI, Pittsburgh Sleep Quality Index; TIA, transient ischemic attack.

Table 4-4. *Evaluation Metrics for Random Forest Models Discriminating the Target Clinical Cohort from a Benchmark Sample of Cognitively Normal Controls*

RF Model	AUC	Accuracy	Precision	Recall	F_1 Score
RG1: Discriminating SCI from CN	0.89	0.79	0.94	0.58	0.72
RG2: Discriminating MCI from CN	0.88	0.76	0.75	0.95	0.84
RG3: Discriminating AD from CN	0.98	0.88	0.98	0.73	0.84

Note. Evaluation metrics reflect average performance of the RF classification model across the five cross-validation folds. Each evaluation metric ranges between 0-1 (higher values denote better performance; See Methods section for further details). Abbreviations: RG, research goal; RF, random forest; AUC, area under the receiver operating characteristic curve; SCI, subjective cognitive impairment; CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease.

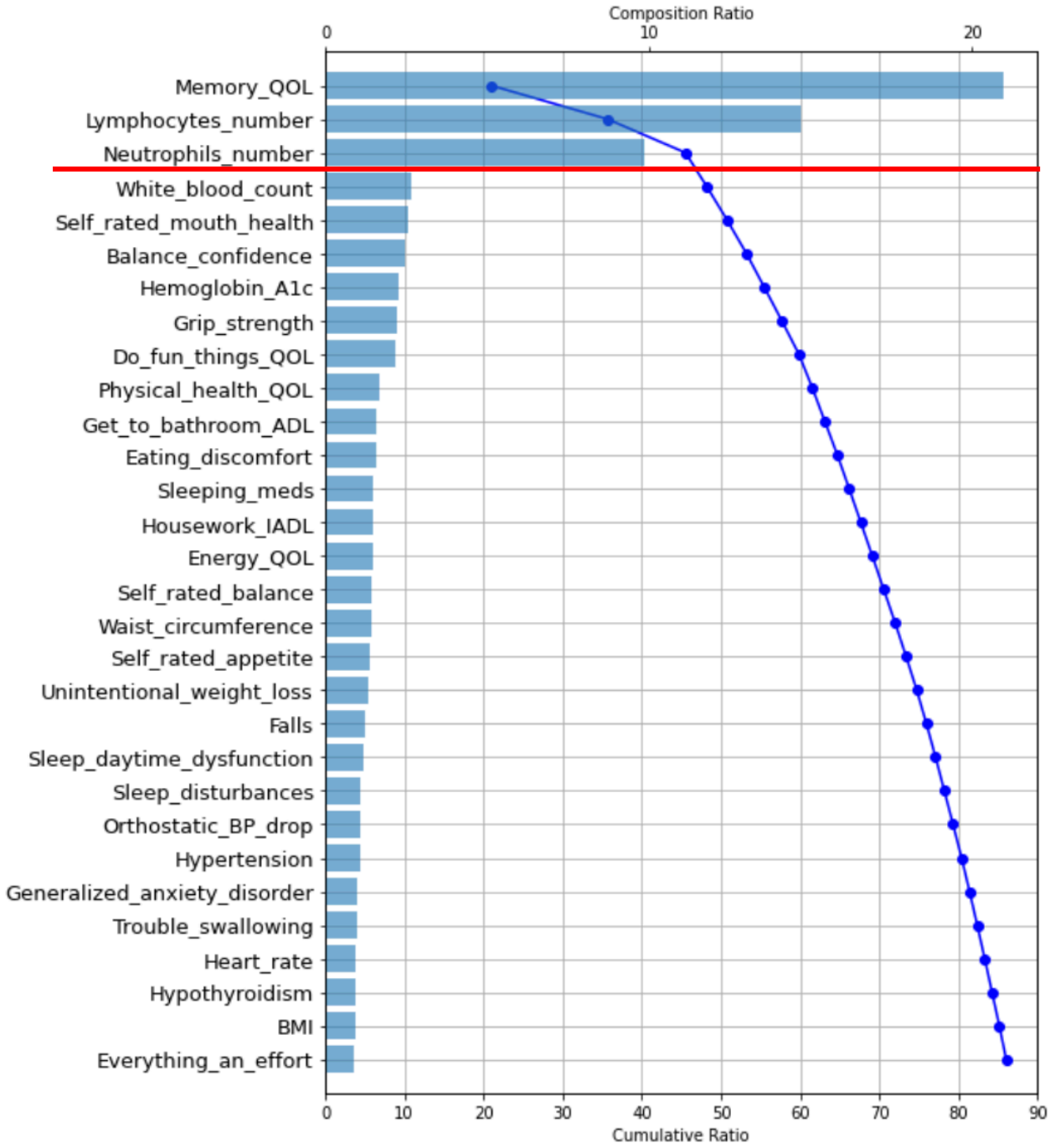


Figure 4-1. Waterfall plot depicting the top 30 predictors that discriminate older adults with subjective cognitive impairment from cognitively normal controls. Predictors are plotted in descending order of contribution to the final classification model. The bars depict the individual composition ratio (i.e., the amount that each predictor contributes to the final classification model;

see top of the figure for scale). The curved line represents the cumulative ratio (i.e., the total amount that each successive predictor contributes to the final classification model; see bottom of the figure for scale). The topmost important predictors are denoted above the red line. Abbreviations: QOL, quality of life; ADL, activities of daily living; IADL, instrumental activities of daily living; BP, blood pressure; BMI, body mass index.

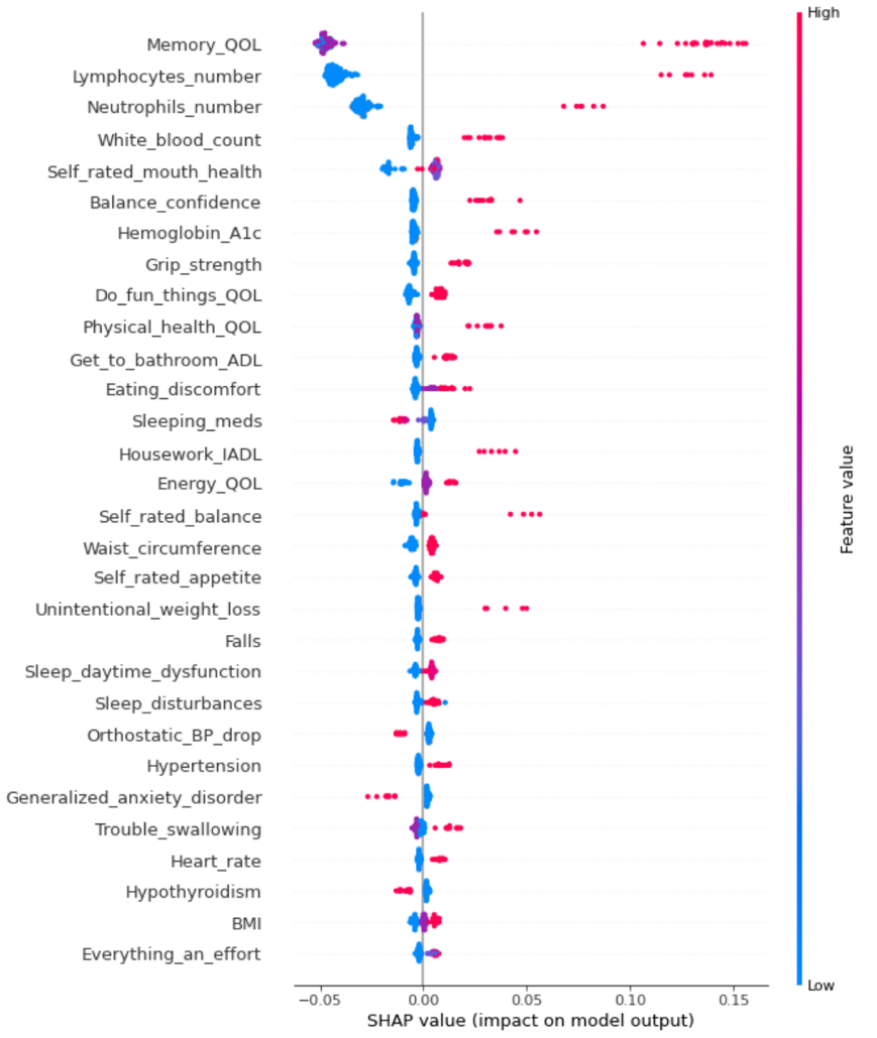


Figure 4-2. Summary plot for the top 30 predictors that distinguish older adults with subjective cognitive impairment (SCI) from cognitively normal controls. Predictors are presented in descending order of impact on model output (i.e., prediction of SCI). Each dot represents one study participant. These dots collectively represent the direction and magnitude of each predictor's effect (see Methods section for further details). Abbreviations: QOL, quality of life; ADL, activities of daily living; IADL, instrumental activities of daily living; BP, blood pressure; BMI, body mass index.

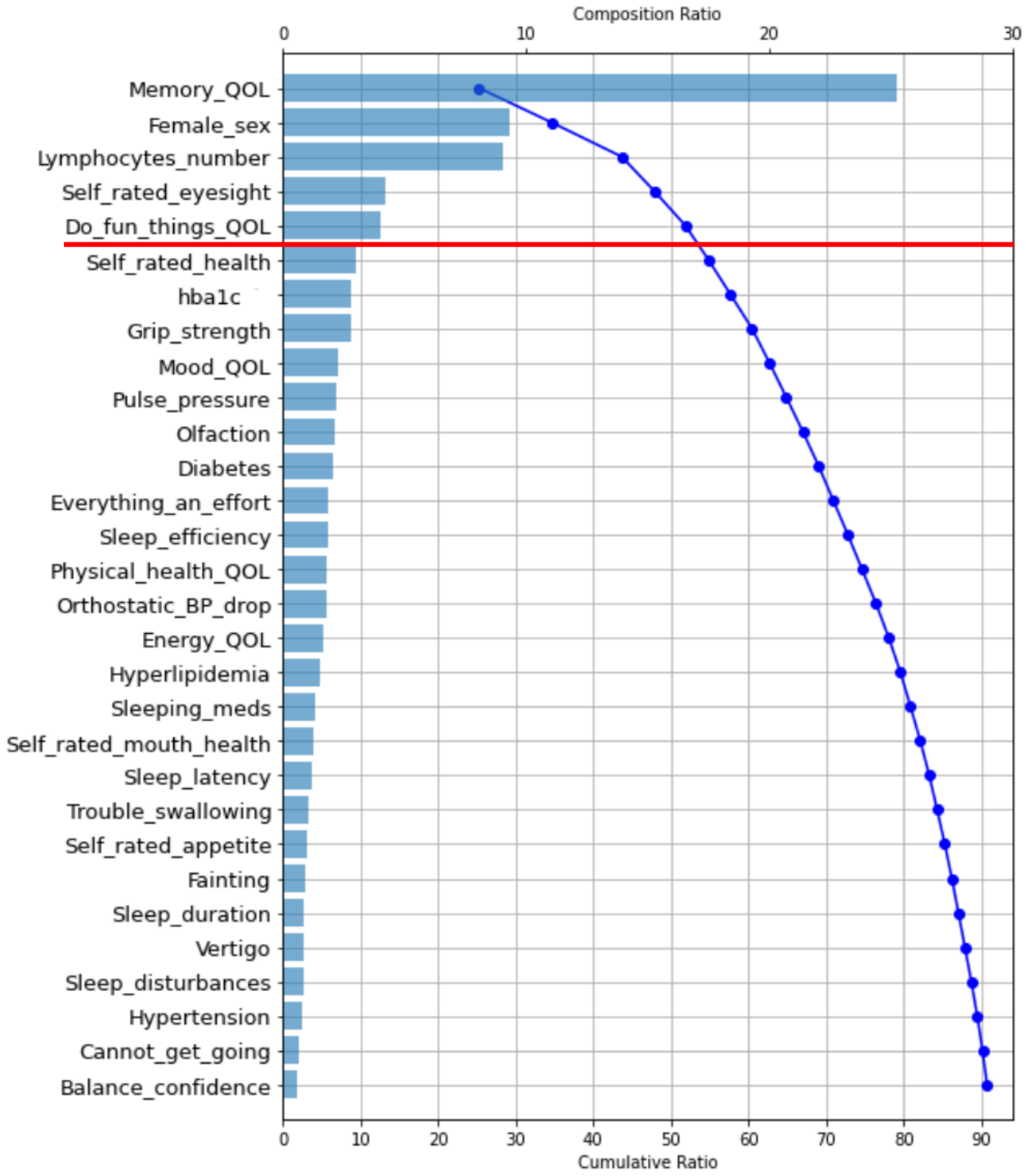


Figure 4-3. Waterfall plot depicting the top 30 predictors that discriminate older adults with mild cognitive impairment from cognitively normal controls. Predictors are plotted in descending order of contribution to the final classification model. The bars depict the individual composition ratio (i.e., the amount that each predictor contributes to the final classification model; see top of the

figure for scale). The curved line represents the cumulative ratio (i.e., the total amount that each successive predictor contributes to the final classification model; see bottom of the figure for scale). The top predictors are denoted above the red line. Abbreviations: QOL, quality of life; hba1c, hemoglobin A1C; BP, blood pressure; Meds, medication.

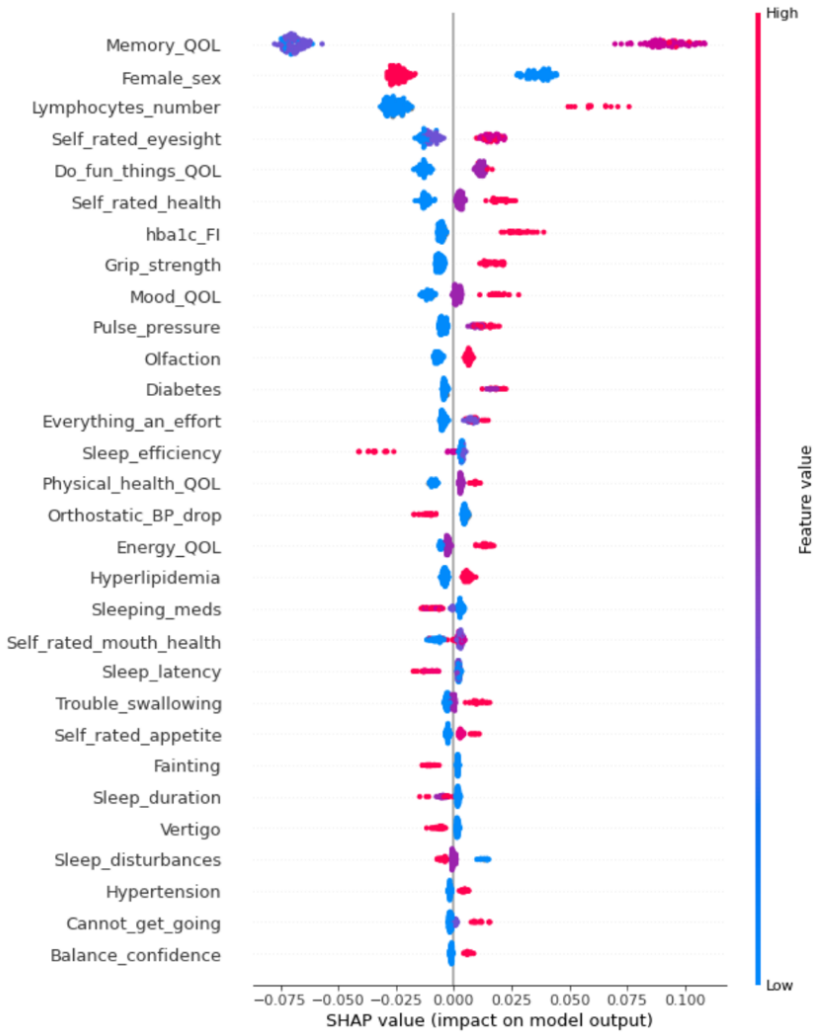


Figure 4-4. Summary plot for the top 30 predictors that distinguish older adults with mild cognitive impairment (MCI) from cognitively normal controls. Predictors are presented in descending order of impact on model output (i.e., prediction of MCI). Each dot represents one study participant. These dots collectively represent the direction and magnitude of each predictor's effect (see Methods section for further details). Abbreviations: QOL, quality of life; hba1c, hemoglobin A1C; BP, blood pressure; Meds, medication.

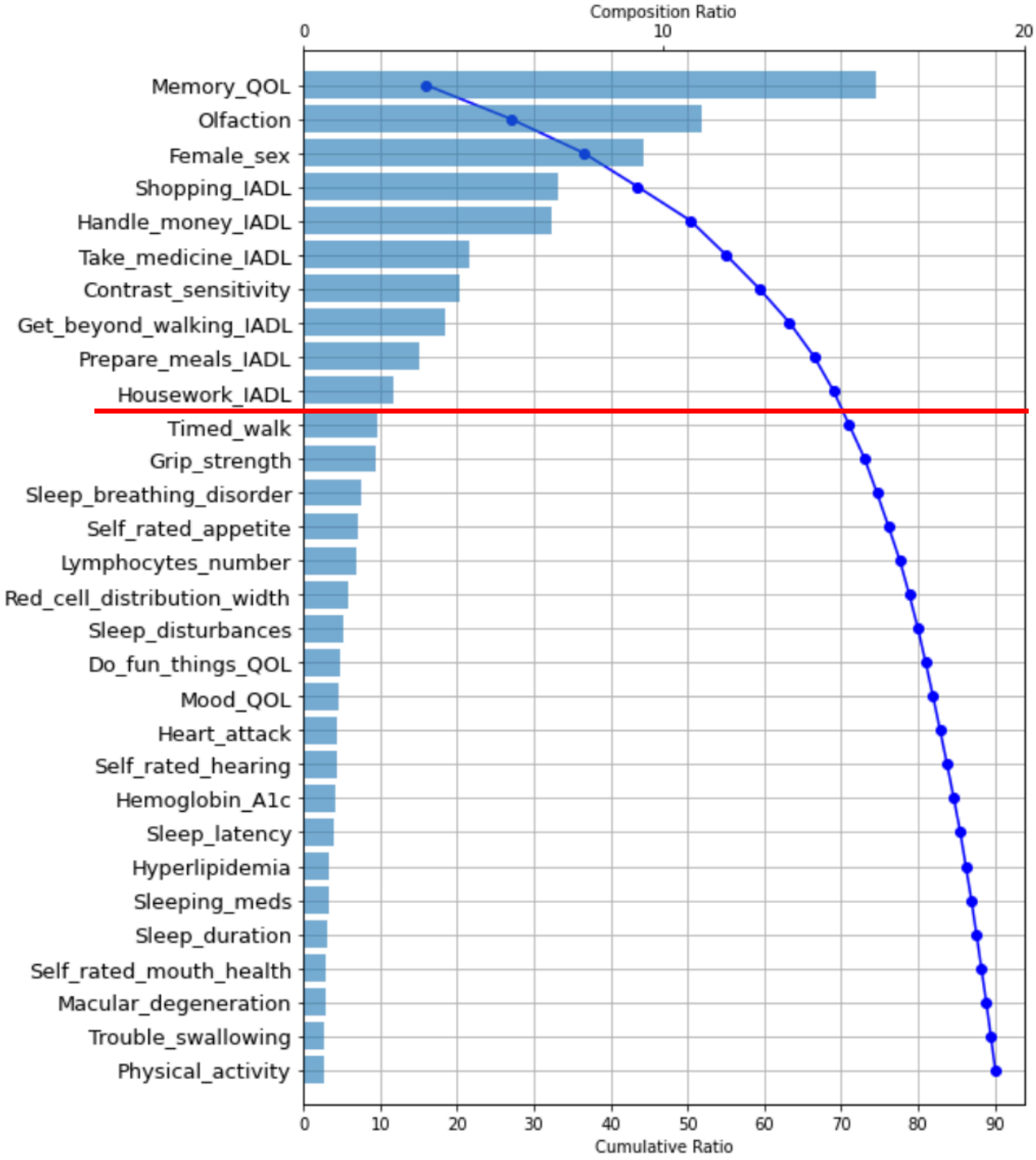


Figure 4-5. Waterfall plot depicting the top 30 predictors that discriminate older adults with Alzheimer's disease from cognitively normal controls. Predictors are plotted in descending order of contribution to the final classification model. The bars depict the individual composition ratio (i.e., the amount that each predictor contributes to the final classification model; see top of the figure for

scale). The curved line represents the cumulative ratio (i.e., the total amount that each successive predictor contributes to the final classification model; see bottom of the figure for scale). The top predictors are denoted above the red line. Abbreviations: QOL, quality of life; IADL, instrumental activities of daily living.

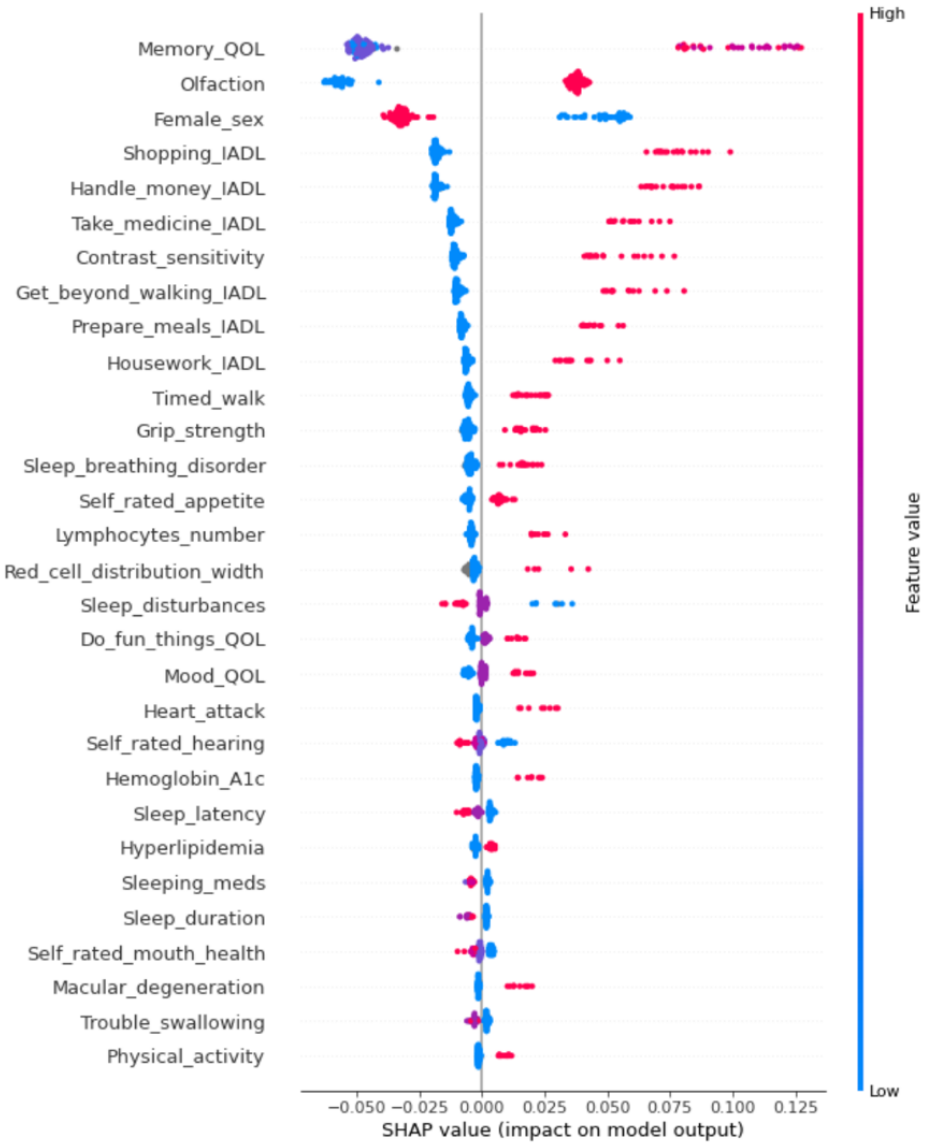


Figure 4-6. Summary plot for the top 30 predictors that distinguish older adults with Alzheimer's disease (AD) from cognitively normal controls. Predictors are presented in descending order of impact on model output (i.e., prediction of AD). Each dot represents one study participant. These dots collectively represent the direction and magnitude of each predictor's effect (see Methods section for further details). Abbreviations: QOL, quality of life; IADL, instrumental activities of daily living.

Chapter 5: General Discussion

The dissertation research applied data-driven and person-centered analytical techniques to three large-scale epidemiological databases in order to accomplish two overarching research aims. First, we sought to develop an unbiased approach to frailty measurement and conceptualization that may contribute to the resolution of contradictions or inconsistencies among prevailing frailty models and research approaches (Fried et al., 2001; Mitnitski et al., 2001). Second, we aimed to detect data-driven frailty profiles or features that signal an increased risk for more rapid and widespread deficit accumulation and/or exacerbated cognitive decline, impairment, and dementia. We addressed these research aims in a series of three programmatic studies, as detailed in the foregoing chapters. The focus of the present chapter is on providing an integrative review of the methodological approaches and findings stemming from the dissertation research, as well as highlighting potential future directions for this line of investigation.

In Study 1 (Bohn et al., 2021), we employed data-driven and person-centered analytic techniques in order to test whether (a) early frailty profiles could be empirically determined at baseline in a large sample of cognitively normal (CN) older adults from the Victoria Longitudinal Study (n = 649); (b) the extracted profiles were differentially related to level and change trajectories in frailty and neurocognitive speed across a 40-year band of aging; and (c) the profile and prediction patterns were robust across sex. We examined these research aims in a series of analytical phases. In the first phase, we applied exploratory factor analysis to 50 baseline multi-morbidity indicators and identified the following frailty-related domains of aging morbidity: *mobility* (e.g., timed turn, use of a mobility aid, grip strength), *instrumental health* (e.g., health has affected ability to do chores, hobbies, get around town), *emotional well-being* (e.g., boredom, depression, loneliness), *comorbidity* (e.g., gastrointestinal problems, bladder trouble, anemia),

respiratory symptoms (e.g., feeling short of breath, asthma, bronchitis), *cardiac symptoms* (e.g., high blood pressure, stroke, heart trouble), and *physical activity* (e.g., arthritis, physical recreation activities, spinal condition). In the second phase, we submitted the proportion of deficits accumulated in each domain to latent profile analysis. Findings revealed three differentiable frailty profiles, including: (a) *not-clinically frail* (*n* = 542, 84%; (b) characterized by minimal impairment across domains), (c) *mobility-type frailty* (*n* = 59, 9%; (d) characterized by impaired mobility function), and (e) *respiratory-type frailty* (*n* = 48, 7%; (f) characterized by impaired respiratory function).Whereas the foremost profile has been reliably documented in related research (Liu et al., 2017; Looman et al., 2018; Olaya et al., 2017; Sadiq et al., 2018), the latter two profiles are consistent with emerging evidence suggesting that mobility (Chhetri et al., 2017; Sarksian et al., 2008; Sourial et al., 2012) or respiratory deficits (Pikoula et al., 2019) may aggregate to form a unique data-driven subtype. We extend prior research by extracting these subtypes from much broader range of aging morbidity measures and validating them as early frailty profiles.

The third analytical phase was comprised of two interrelated steps. In the first step, we assembled three waves of data for a 50-item frailty index (Thibeau et al., 2019) and tested longitudinal trajectories stratified by baseline frailty profiles. Findings showed that older adults with mobility- or respiratory-type frailty not only had the highest frailty index levels, but they also showed more rapid frailty progression as compared to not-clinically frail older adults. Notably, individuals classified as having mobility-type frailty also evinced a faster rate of deficit accumulation as compared to individuals with respiratory-type frailty. These findings converge with earlier research reporting positive associations between frailty progression and single indicators of mobility (Doi et al., 2018; Fallah et al., 2011) or respiratory function (Pollack et al., 2017; Vaz Fragoso et al., 2012). We advance these studies by proposing and validating a portal

approach to frailty emergence and progression. Specifically, we demonstrated that frailty profiles characterized by impaired mobility or respiratory function may serve as gateways to classifiable global frailty, which then cascades into more rapid and widespread deficit accumulation. In the second step, we assembled longitudinal data for a latent neurocognitive speed variable and tested cognitive trajectories stratified by baseline frailty profiles. Consistent with the foregoing pattern, we found that (a) older adults with mobility- or respiratory-type frailty trended towards worse performance relative to not-clinically frail older adults and (b) older adults with mobility-type frailty evinced the fastest rate of neurocognitive slowing, followed in order by respiratory-type frailty, and then not-clinically frail. To our knowledge, this study is the first to determine data-driven early frailty profiles and validate them against prediction of cognitive aging trajectories. Our results suggest that distinct configurations of aging morbidity marked by impaired mobility or respiratory function may have differential effects on frailty progression and neurocognitive slowing. Proper assessment and management of these signs, symptoms, and diseases in clinical-research settings is therefore encouraged. In the fourth phase, we tested and confirmed that the frailty profiles and prediction patterns generalized across sex. We reasoned that sex differences may be more likely to appear in later life or more serious frailty conditions. Because limited work has examined these research aims (Liu et al., 2017; Looman et al., 2018; Sadiq et al., 2018; Segaux et al., 2019) and the earlier findings reported are equivocal, we identified this as an important target for follow-up research.

In Study 2, we assembled longitudinal big data from the National Alzheimer's Coordinating Center. The general goal was to extend the approach of Study 1 to a wider range of clinical cohorts, a different profile of measurement occasions, and a broad spectrum of morbidity indicators and predictors. Specifically, we assembled baseline and 2-year follow-up data for 43 deficits

representing the heterogeneity of frailty in two related clinical cohorts of older adults, including amnestic mild cognitive impairment (aMCI; baseline n = 878) and Alzheimer's disease (AD; baseline n = 2,196). We subsequently applied latent transition analysis (a longitudinal extension of latent profile analysis) to data for the entire study sample in order to (a) detect underlying clusters (or statuses) of aging multi-morbidity across measurement occasions; (b) characterize patterns of frailty transitions; and (c) examine frailty emergence and progression in relation to nonmodifiable (e.g., sex) and potentially modifiable risk characteristics (e.g., clinical cohort).

We examined these research aims in a series of four analytical phases. In the first phase, we applied exploratory factor analysis to the aging morbidity indicators and identified the following frailty-related domains that were interpreted as *ambulatory ability* (e.g., slowing of motor movements, tremor, incontinence), *instrumental health* (e.g., difficultly turning off stove, traveling out of the neighbourhood, playing a game of skill), *emotional well-being* (e.g., boredom, helplessness, life satisfaction), *cardiovascular symptoms* (e.g., hypercholesterolemia, hypertension, diabetes), and *behavioral disturbances* (e.g., appetite changes, nighttime behaviors, agitation or aggression). Notably, these domains and the corresponding indicators harmonize with those detected in Study 1 (Bohn et al., 2021). In the second phase, we conducted latent transition analysis, which involved the following sequence of steps: (a) conduct a separate latent profile analysis at each time point; (b) establish longitudinal measurement invariance; (c) examine unconditional latent transition probabilities; and (d) perform prediction analyses. To our knowledge, only one study has examined heterogeneity in frailty emergence and progression using latent transition analysis (Lafortune et al., 2009), with results suggesting that this is a promising approach. Importantly, however, this study was limited by a focus on CN older adults and a narrow breadth of aging morbidity indicators.

In the first step of our analyses, we detected two differentiable baseline frailty, including *Not-Clinically Frail* (*n* = 2,790, 91%) and *Moderately Frail* (*n* = 284, 9%). At follow-up, we again detected the *Not-Clinically Frail* (*n* = 1,714; 56%) and *Moderately Frail* statuses (*n* = 571; 19%), as well as two additional statuses representing participants who were *Mildly Frail* (*n* = 654; 21%) or *Severely Frail (n* = 135; 4%). We tested and confirmed in longitudinal measurement invariance tests that the *Not-Clinically Frail* and *Moderately Frail* statuses retained their substantive interpretations over time. Interestingly, the pattern of mean differences observed across statuses and the resulting interpretations align with those reported in Study 1 (Bohn et al., 2021). Specifically, the Not-Clinically Frail status was characterized at baseline and follow-up by (a) relatively limited impairment across the considered domains of aging morbidity, (b) the lowest scores on an independently calculated 43-item frailty index, and (c) the highest prevalence. In Study 1, we noted that this pattern would be expected in a relatively healthy and CN aging group. Results from Study 2 suggest that this pattern may also be expected in aging samples characterized by cognitive impairment or dementia, albeit to a lesser extent with advancing age and severity of cognitive impairment. These findings validate the growing literature suggesting that frailty and cognitive impairment are related constructs that mutually interact but may not inevitably co-occur (Burt et al., 2019; Kojima et al., 2017; Robertson et al., 2013). The Mildly, Moderately, and Severely Frail statuses were characterized by successively higher levels of ambulatory impairment and higher frailty burdens on a 43-item index. When taken together with Study 1 findings, our results suggest that mobility deficits are a defining characteristics of data-driven frailty subtypes across the spectrum of normal cognitive aging, impairment, and dementia.

In the third phase, we examined unconditional latent transition probabilities and detected significant heterogeneity in frailty progression, including stability, progression, and reversion. This

study is the first to our knowledge to distinguish and track frailty statuses in a large sample of older adults with a diagnosis of aMCI or AD based on prevailing diagnostic criteria (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). We note two specific ways in which these findings advance the emerging literature on frailty transitions and trajectories (O'Caoimh et al., 2018; Rohrmann, 2020; Welstead et al., 2020). First, our results demonstrate that reversion of frailty is possible not only in unimpaired aging groups but also in older adults who have been characterized by cognitive impairment or dementia. Several recent reviews have highlighted that spontaneous clinical remission of frailty remains scarcely considered and identified this as a priority area (Canevelli et al., 2017; Ofori-Asenso et al., 2019). Our results respond to this challenge. Second, our results showed that Moderately Frail older adults are more likely be classified at follow-up into frailty statuses characterized by a higher frailty burden as compared to Not-Clinically Frail older adults. This pattern indicates that (a) there is a lower likelihood of reversing or attenuating frailty once the disability cascade is fully established (Canevelli et al., 2017) and (b) older adults presenting with higher levels of ambulatory (or mobility) impairment may be at an increased risk for adverse frailty transitions or trajectories (as was also depicted in Study 1; Bohn et al., 2021). These results collectively suggest that, across the AD spectrum, early and targeted interventions may be required for older adults presenting with mobility and related functional complaints. Future studies could examine whether rehabilitation and pharmacologic treatments targeting these deficits may offset or delay frailty progression and adverse cognitive aging outcomes.

The fourth phase of our analyses was comprised of two interrelated steps. Specifically, we characterized and validated the detected latent statuses by examining non-modifiable and potentially modifiable risk factors as predictors of (a) baseline membership and (b) the probability of transitioning across latent frailty statuses. Results from the first step indicated that male sex, AD

diagnosis, poorer global cognition, and older age increased risk for classification into the Moderately Frail status at baseline. Notably, the latter three predictors were not examined in Study 1 (Bohn et al., 2021) and the conditional direct effect of clinical cohort (based on prevailing diagnostic criteria) and global cognitive function on classification into data-driven frailty statuses remains scarcely considered. Our results suggest that future research should examine the dissociable effects of these predictors on frailty subtype emergence and progression. It is interesting that the present results for sex diverged those from Study 1 (Bohn et al., 2021), where we reported that males and females were equally likely to be classified as having mobility-type frailty, respiratory-type frailty, or as not-clinically frail. Nevertheless, follow-up analyses from Study 2 confirmed our supposition that sex differences may be more likely to appear in later life or more serious frailty conditions. Specifically, participants in Study 2 were comparatively older and frailer than Study 1 participants. Results from the second step of this analytical phase revealed that select latent transition probabilities varied as a function of baseline risk characteristics, including chronological age and *APOE* carrier status. The direction of effects for *APOE* ran in contrast to our expectations, such that carriers of the ε4 risk allele were less likely to experience adverse frailty transitions. Limited literature has examined *APOE*-frailty associations and the results are equivocal (Bai et al., 2021; Rockwood et al., 2008; Thibeau et al., 2019; Ward et al., 2021a). However, at least one other study has suggested a possible protective effect of *APOE* (Kulminski et al., 2008), whereby female carriers of the ε4/ε4 allele were less likely to experience severe impairment in activities of daily living as compared to non-carriers. We therefore identify this as a priority area for follow-up research.

In summary, Study 1 (Bohn et al., 2021) and 2 of the dissertation research suggest that prevailing approaches that collapse across multiple systems of aging morbidity may mask

important heterogeneity in (a) frailty emergence and progression and (b) risk for adverse cognitive aging outcomes. Specifically, in each of these studies we highlighted that data-driven approaches to frailty measurement and conceptualization may elucidate clusters of characteristics that (a) serve as morbidity-intensive portals into broader and chronic frailty or (b) are associated with exacerbated cognitive decline, impairment, and dementia. We note that, in each of the foregoing studies, we applied data-driven data-reduction techniques to a range of aging morbidity indicators (n = 40–50) in order to produce separable health domains. We subsequently calculated the proportion of deficits accumulated in each domain and applied person-centered and data-driven analytical techniques to these summary measures. In Study 3, we advance the methodological approach of Studies 1 and 2 by (a) including a wider breadth of aging morbidity indicators, (b) examining the full AD spectrum with multiple clinical cohorts, and (c) applying unbiased machine learning techniques to individual indicators (as opposed to domains). Together, these three methodological advances will help us identify the most important features of frailty that increase risk for negative outcomes across the AD spectrum.

Specifically, in Study 3 we used random forest analysis to test (in a competitive computational context) the relative predictive importance of 84 frailty-related features from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) database in discriminating older adults with subjective cognitive impairment (SCI; n = 36), MCI (n = 116), or AD (n = 43) from a benchmark sample of CN controls (n = 60). Thus, whereas Studies 1 and 2 separately considered cohorts of older adults with normal cognition or aMCI and AD, Study 3 examined data-driven frailty assessment across the spectrum of normal cognitive aging, through to impairment and AD-related dementia. Recent research examined the prevalence of frailty in the COMPASS-ND database using an 81-item frailty index (Burt et al., 2019). We contribute to this

work by (a) testing aging morbidity indicators that were not previously considered (e.g., fluid biomarkers), (b) calculating a 30-item data-driven frailty index for each clinical cohort using random forest analysis results, and (c) examining whether frailty levels varied across cohorts and complementary operationalizations of a frailty index.

In the first phase of our analyses, we conducted a series of three pairwise random forest comparisons. Results indicated that each classification model reliably discriminated the target clinical cohort (SCI, MCI, or AD) from the benchmark sample of CN controls. These findings (a) converge with Studies 1 and 2, where we reported significant associations between data-driven frailty classifications, neurocognitive slowing, global cognition, and clinical cohort (aMCI, AD) and (b) extend previous work identifying frailty as risk factor for SCI (Gifford et al., 2019) and MCI (Borges et al., 2019b). Further, our results clarify the inconsistent evidence on frailty-dementia associations and suggest that, when a multidomain deficit accumulation approach is employed as the operational definition, frailty increases AD risk.

Examination of prediction patterns across clinical cohorts revealed several important findings. For example, across random forest classification models, the top 30 features explained 90% of the model's output. These results suggests that increased integration of data-driven frailty assessment into clinical-research settings may facilitate accurate identification of at-risk older adults and the development of optimized care plans. Further, we identified the following features as central risk elevating characteristics for SCI, MCI, and/or AD. With respect SCI, poorer quality of life (memory), abnormal lymphocyte counts, and abnormal neutrophil counts were leading discriminative features. With respect to MCI, poorer quality of life (memory, leisure), male sex, abnormal lymphocyte counts, and poorer self-rated eyesight were leading discriminative features. With respect to AD, poorer quality of life (memory), sensory deficits (olfaction and visual contrast

sensitivity), male sex, and higher levels of dependence in instrumental activities of daily living (ability to go shopping, handle money, take medication, get to places beyond walking distance, prepare meals, and perform housework) were leading discriminative features. Importantly, we also determined that the following domains of deficits varied in terms of their contribution to the random forest classification models but nonetheless generalized across prediction of SCI, MCI, and AD: quality of life (memory, leisure), inflammatory biomarkers (lymphocytes, glycated hemoglobin), sleep (disturbances, medication), and oral health and nutritional factors (self-reported appetite, mouth health, difficulty swallowing), and functional indicators (grip strength). The latter finding dovetails with Study 1 (Bohn et al., 2021) and 2, and bolsters the notion that mobility and related functional impairments may serve as harbingers of adverse frailty-related outcomes.

Results stemming from our random forest classification analyses contribute to and extend the literature on frailty measurement and conceptualization in the following ways. First, accumulating evidence suggests that indicators of peripheral systemic inflammation may represent promising biomarkers of frailty (Collerton et al., 2012; Rodriguez-Mañas et al., 2020; Wang et al., 2019) and have advocated for including such deficits in the operational definition of frailty (Blodgett et al., 2017; Howlett et al., 2014; Mitnitski et al., 2015; Rockwood et al., 2015). Our results buttress these claims. Second, the varied nature of these domains suggests that (a) multi-domain deficit accumulation approaches better capture the typical heterogeneity of frailty as compared to syndromic definitions and (b) composite index approaches may increase prediction accuracy by incorporating these features into the operational definition.

Importantly, we also detected frailty-related features that were selectively sensitive to prediction of SCI (e.g., unintentional weight loss, white blood cell count), MCI (e.g., self-reported eyesight, pulse pressure), and AD (e.g., timed walk, self-reported hearing). These results may

inform precision medicine by highlighting critical components of frailty that could be selectively targeted across the AD spectrum for the twin purposes of preventing or ameliorating frailty and risk for adverse cognitive aging outcomes. Accordingly, we calculated a separate data-driven frailty index for each clinical cohort using data for the top 30 features identified in machine learning analyses. Subgroup analyses revealed that older adults with SCI, MCI, or AD reported comparable levels of frailty across the 30-item data-driven index and the 81-item index (Burt et al., 2019). However, each of the respective clinical cohorts reported higher levels of frailty on the 30-item index as compared to CN controls and the 81-item index. To our knowledge, this study is the first to calculate a data-driven frailty index and systematically examine whether frailty levels vary across the AD spectrum and complementary conceptualizations of a frailty index. Establishing reliable estimates of the prevalence of frailty (e.g., values on the frailty index ≥ 0.25) in cognitively impaired or demented samples has applications for developing frailty prevention and treatment programs. In Study 2, we reported that older adults with aMCI endorsed an average value on the 43-item frailty index of 0.15, whereas participants with AD endorsed a comparatively higher level at 0.27. In Study 3, the average value reported on the 81-item index was 0.18 for SCI, 0.20 for MCI, and 0.21 for AD. Follow-up studies could examine frailty index level and change trajectories and determine whether change in the level of frailty affects cognitive aging trajectories and outcomes (e.g., MCI conversion).

Future Directions

We note several potential future directions for follow-up research stemming from Study 1 (Bohn et al., 2021). First, our focus on detecting early manifestations of frailty profiles and the representation of these as portals into global frailty and exacerbated neurocognitive slowing is a promising area of continued research interest. In future studies, we could test the detected data-

driven frailty profiles as predictors of additional frailty-related outcomes, such as falls and hospitalization. Second, latent transition analysis could be applied to longitudinal multi-morbidity data from the Victoria Longitudinal Study in order to (a) determine whether additional frailty classifications can be empirically determined at follow-up in a large sample of CN older adults and (b) characterize patterns of frailty transitions. Third, additional risk and protection factors could be extracted from this heterogeneous database and subsequently tested as predictors of baseline classifications and patterns of frailty progression.

With respect Study 2, we previously noted that were surprised to find that a relatively limited number of risk characteristics predicted frailty progression. That is, the likelihood of transitioning across frailty statuses did not vary according to sex (male or female), race/ethnicity (non-Hispanic White or Black/African American), clinical cohort (aMCI or AD), global cognition (performance on the Mini Mental State Exam or an equivalent measure), or educational background (total years). Although this pattern of (null) results is consistent with the literature on latent transition analysis (e.g., Collins & Lanza, 2010) and related studies employing this analytical approach (e.g., Ryoo et al., 2018), we believe that this study would be strengthened by the identification of significant predictors of latent transition probabilities. As such, we plan to re-review the NACC database and test theoretically relevant nonmodifiable and potentially modifiable characteristics as predictors of baseline frailty classifications and transitions. This research direction, together with those outlined for Study 1, may reveal novel and important precision targets for preventing adverse frailty transitions and related outcomes across the spectrum of normal cognitive aging, impairment, and dementia.

With respect to Study 3, we previously noted that we were unable to conduct random forest analyses as stratified by sex due to the relatively small and/or imbalanced subsample sizes in the

COMPASS-ND database. In the interim, we examined whether the risk for SCI, MCI, and AD varied across sex, with results suggesting that males were at an increased risk for the latter two outcomes. Importantly, we anticipate that, following an upcoming data release, our study will be sufficiently powered to examine whether prediction patterns vary for males as compared to females. A small number of frailty-related and cognitive aging studies have performed random forest analyses as stratified by sex (Greene et al., 2014; McFall et al., 2019; Peng et al., 2020), with results suggesting that this is a promising research direction. Findings from this line of investigation may (a) reveal sex differences in the frailty-related features or domains of deficits that elevate clinical risk across the AD spectrum and (b) advance understanding of sex differences in the underlying pathophysiologic mechanisms of frailty.

Significance and Conclusion

In summary, the dissertation research demonstrated in a series of three programmatic studies that person-centered and data-driven analytic technologies may contribute to the resolution of empirical and clinical inconsistencies between prevailing frailty models and research approaches by identifying clusters of frailty-related deficits or individual features that serve as portals into broader and chronic frailty and/or exacerbated cognitive decline, impairment, and dementia. In Study 1 (Bohn et al., 2021), we assembled data for a large sample of CN older adults and subsequently (a) distinguished data-driven frailty profiles characterized by mobility or respiratory deficits and (b) demonstrated differential associations between these modalities and trajectories of frailty index progression and neurocognitive slowing. In Study 2, we assembled big data for older adults with aMCI or AD and subsequently (a) detected longitudinal data-driven frailty statuses characterized by varying levels of ambulatory impairment, (b) revealed heterogeneity in frailty progression, and (c) demonstrated that baseline risk characteristics (e.g., clinical cohort and global

cognition) were differentially related to classification into data-driven frailty statuses. In Study 3, we assembled data for older adults who spanned the AD spectrum and subsequently (a) identified selected important frailty-related features that elevated clinical risk for SCI, MCI, and/or AD and (b) examined frailty levels across cohorts and complementary conceptualizations of a frailty index. Collectively, these results highlight critical domains of aging morbidity (e.g., mobility and related functional indicators) that should be targeted and tracked early in the clinical course of frailty in an effort to prevent adverse outcomes.

We note several potential future directions for the emerging literature on data-driven approaches to frailty operationalization and prediction of adverse outcomes. First, in each of the foregoing studies we demonstrated significant associations between data-driven frailty classifications and cognitive status or performance. We highlighted several potential explanatory mechanisms for these associations (e.g., hormonal dysregulation, nutritional factors and deficiencies, chronic inflammation, cardiovascular risks) and linked these explanations to relevant literature (Canevelli et al., 2015; Panza et al., 2015; Robertston et al., 2013). However, because we did not explicitly test these mechanisms and previous reviews have identified this as a priority area (Canevelli et al., 2015; Robertson et al., 2013), we note that future studies are required to establish the pathophysiologic underpinnings of frailty-cognition associations. Second, our results suggest that, while older adults presenting with mobility or ambulatory complaints may be particularly vulnerable to adverse frailty transitions or trajectories, reversion of frailty remains possible, even amongst older adults characterized with cognitive impairment or dementia. Future studies should determine whether precision interventions targeting these deficits (and related functional impairments) early in the clinical course of frailty may reverse or attenuate frailty progression and have downstream effects on reducing differential cognitive decline and impairment, as well as

related negative outcomes. Third, sparse large-scale, longitudinal epidemiological research has sought to produce some resolution of the various empirical and clinical inconsistencies between prevailing frailty models using powerful machine learning technologies. We noted in our review that the majority of available machine learning research is predicated on the frailty phenotype or accumulation of deficits approach, whereas relatively few studies have developed random forest classification models using well-defined surrogates for frailty. Accordingly, we encourage future validation studies to perform random forest prediction analyses across a broader range of (a) clinical cohorts (e.g., non-AD dementia), (b) aging morbidity indicators (e.g., fluid biomarkers), and (c) frailty-related outcomes (e.g., adverse cognitive aging trajectories). Fourth, a paucity of data-driven frailty research has examined whether frailty classifications and prediction patterns vary across important stratification variables, including age, sex, and race/ethnicity. This approach may reveal novel precision targets for frailty assessment, prevention, and prognostication in clinical-research settings. In sum, we identify this line of investigation as a profitable area of continued research attention for the prevention or treatment of frailty and related adverse outcomes.

References

Aguayo, G. A., Donneau, A. F., Vaillant, M. T., Schritz, A., Franco, O. H., Stranges, S., Malisoux, L., Guillaume, M., & Witte, D. R. (2017). Agreement between 35 published frailty scores in the general population. *American Journal of Epidemiology*, *186*(4), 420–434. https://doi.org/10.1093/aje/kwx061

Al Saedi, A., Feehan, J., Phu, S., & Duque, G. (2019). Current and emerging biomarkers of frailty in the elderly. *Clinical Interventions in Aging*, *14*, 389–398. https://doi.org/10.2147/CIA.S168687

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, 7(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

Alzheimer's Association. (2016). 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *12*(4), 459–509. https://doi.org/http://dx.doi.org/10.1016/j.jalz.2016.03.001

Alzheimer's Association. (2019). 2019 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *15*(3), 321–387. https://doi.org/10.1016/j.jalz.2019.01.010

Alzheimer Society. (2010). *Rising tide: The impact of dementia on Canadian Society*. Alzheimer Society of Canada.

Alzheimer Society of Canada. (2016). *Prevalence and monetary costs of dementia in Canada*. Alzheimer Society of Canada.

Amieva, H., le Goff, M., Millet, X., Orgogozo, J. M., Pérès, K., Barberger-Gateau, P., Jacqmin-Gadda, H., & Dartigues, J. F. (2008). Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. *Annals of Neurology*, *64*(5), 492–498. https://doi.org/10.1002/ana.21509

Andrew, M. K., & Tierney, M. C. (2018). The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men? *Women's Health*, *14*, 1–8. https://doi.org/10.1177/1745506518817995

Anstey, K. J., & Dixon, R. A. (2014). Applying a cumulative deficit model of frailty to dementia: Progress and future challenges. *Alzheimer's Research & Therapy*, *6*(84), 1–3. https://doi.org/http://alzres.com/content/6/9/84

Anstey, K. J., Ee, N., Eramudugolla, R., Jagger, C., & Peters, R. (2019). A systematic review of meta-analyses that evaluate risk factors for dementia to evaluate the quantity, quality, and global representativeness of evidence. *Journal of Alzheimer's Disease*, *70*(s1), S165–S186. https://doi.org/10.3233/JAD-190181

Anstey, K. J., Eramudugolla, R. E., Hosking, D. E., Lautenschlager, N. T., & Dixon, R. A. (2015). Bridging the translation gap: From dementia risk assessment to advice on risk reduction. *The Journal of Prevention of Alzheimer's Disease*, *2*(3), 189–198. https://doi.org/10.14283/jpad.2015.75

Apóstolo, J., Cooke, R., Bobrowicz-Campos, E., Santana, S., Marcucci, M., Cano, A., Vollenbroek-Hutten, M., Germini, F., D'Avanzo, B., Gwyther, H., & Holland, C. (2018). Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports*, *16*(1), 140–232. https://doi.org/10.11124/JBISRIR-2017-003382

Arevalo-Rodriguez, I., Smailagic, N., Roquéi Figuls, M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O. L., Bonfill Cosp, X., & Cullum, S. (2015). Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database of Systematic Reviews*, *2015*(3), 1–76. https://doi.org/10.1002/14651858.CD010783.pub2

Armstrong, J. J., Mitnitski, A., Andrew, M. K., Launer, L. J., White, L. R., & Rockwood, K. (2015). Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: A multistate modeling approach. *Alzheimer's Research and Therapy*, *7*(38), 1–9. https://doi.org/10.1186/s13195-015-0120-7

Artero, S., Ancelin, M. L., Portet, F., Dupuy, A., Berr, C., Dartigues, J. F., Tzourio, C., Rouaud, O., Poncet, M., Pasquier, F., Auriacombe, S., Touchon, J., & Ritchie, K. (2008). Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *Journal of Neurology, Neurosurgery and Psychiatry*, *79*(9), 979–984. https://doi.org/10.1136/jnnp.2007.136903

Asparouhov, T., & Muthén, B. (2014). Auxiliary variables in mixture modeling: Three-step approaches using Mplus. *Structural Equation Modeling: A Multidisciplinary Journal*, *21*(3), 329–341. https://doi.org/10.1080/10705511.2014.915181

Attems, J., Walker, L., & Jellinger, K. A. (2015). Olfaction and aging: A mini-review. *Gerontology*, *61*(6), 485–490. https://doi.org/10.1159/000381619

Avila-Funes, J. A., Carcaillon, L., Helmer, C., Carrière, I., Ritchie, K., Rouaud, O., Tzourio, C., Dartigues, J. F., & Amieva, H. (2012). Is frailty a prodromal stage of vascular dementia? Results from the Three-City Study. *Journal of the American Geriatrics Society*, *60*(9), 1708–1712. https://doi.org/10.1111/j.1532-5415.2012.04142.x

Bai, G., Wang, Y., Kuja-Halkola, R., Li, X., Tomata, Y., Karlsson, I. K., Pedersen, N. L., Hägg, S., & Jylhävä, J. (2021). Frailty and the risk of dementia: Is the association explained by shared environmental and genetic factors? *BMC Medicine*, *19*(248), 1–12. https://doi.org/10.1186/s12916-021-02104-3

Bandeen-Roche, K., Xue, Q. L., Ferrucci, L., Walston, J., Guralnik, J. M., Chaves, P., Zeger, S. L., & Fried, L. P. (2006). Phenotype of frailty: Characterization in the Women's Health and Aging Studies. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61*(3), 262–266. https://doi.org/10.1093/gerona/61.3.262

Bandelow, S., Xu, X., Xiao, S., & Hogervorst, E. (2016). Cluster analysis of physical and cognitive ageing patterns in older people from Shanghai. *Diagnostics*, *6*(11), 1–13. https://doi.org/10.3390/diagnostics6010011

Banerjee, S., Samsi, K., Petrie, C. D., Alvir, J., Treglia, M., Schwam, E. M., & de Valle, M. (2009). What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *International Journal of Geriatric Psychiatry*, *24*(1), 15–24. https://doi.org/10.1002/gps.2090

Barthold, D., Nandi, A., Mendoza Rodríguez, J. M., & Heymann, J. (2014). Analyzing whether countries are equally efficient at improving longevity for men and women. *American Journal of Public Health*, *104*(11), 2163–2169. https://doi.org/10.2105/AJPH.2013.301494

Beekly, D. L., Ramos, E. M., Lee, W. W., Deitrich, W. D., Jacka, M. E., Wu, J., Hubbard, J. L., Koepsell, T. D., Morris, J. C., & Kukull, W. A. (2007). The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. *Alzheimer Disease and Associated Disorders*, *21*(3), 249–258. https://doi.org/10.1097/WAD.0b013e318142774e

Bergman, H., Ferrucci, L., Guralnik, J., Hogan, D. B., Hummel, S., Karunananthan, S., & Wolfson, C. (2007). Frailty: An emerging research and clinical paradigm—issues and controversies. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(7), 731–737. https://doi.org/10.1093/gerona/62.7.731

Besser, L., Kukull, W., Knopman, D. S., Chui, H., Galasko, D., Weintraub, S., Jicha, G., Carlsson, C., Burns, J., Quinn, J., Sweet, R. A., Rascovsky, K., Teylan, M., Beekly, D., Thomas, G., Bollenbeck, M., Monsell, S., Mock, C., Zhou, X. H., … Morris, J. C. (2018). Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set. *Alzheimer Disease and Associated Disorders*, *32*(4), 351-358. https://doi.org/10.1097/WAD.0000000000000279

Bhome, R., Berry, A. J., Huntley, J. D., & Howard, R. J. (2018). Interventions for subjective cognitive decline: Systematic review and meta-analysis. *BMJ Open*, *8*(7), 1–10. https://doi.org/10.1136/bmjopen-2018-021610

Blagosklonny, M. v. (2007). Paradoxes of aging. *Cell Cycle*, *6*(24), 2997–3003. https://doi.org/10.4161/cc.6.24.5124

Bloch, L., & Friedrich, C. M. (2021). Data analysis with Shapley values for automatic subject selection in Alzheimer's disease data sets using interpretable machine learning. *Alzheimer's Research & Therapy*, *13*(155), 1–30. https://doi.org/10.1186/s13195-021-00879-4

Blodgett, J. M., Theou, O., Howlett, S. E., & Rockwood, K. (2017). A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. *GeroScience*, *39*(4), 447–455. https://doi.org/10.1007/s11357-017-9993-7

Blodgett, J. M., Theou, O., Mitnitski, A., Howlett, S. E., & Rockwood, K. (2019). Associations between a laboratory frailty index and adverse health outcomes across age and sex. *Aging Medicine*, *2*(1), 11–17. https://doi.org/10.1002/agm2.12055

Bobak, C. A., McDonnell, L., Nemesure, M. D., Lin, J., & Hill, J. E. (2020). Assessment of imputation methods for missing gene expression data in meta-analysis of distinct cohorts of tuberculosis patients. *Pacific Symposium on Biocomputing*, *25, 307-318.*

Bohn, L., McFall, G. P., Wiebe, S. A., & Dixon, R. A. (2020). Body mass index predicts cognitive aging trajectories selectively for females: Evidence from the Victoria Longitudinal Study. *Neuropsychology*, *34*(4), 388–403. https://doi.org/10.1037/neu0000617

Bohn, L., Zheng, Y., Mcfall, G. P., & Dixon, R. A. (2021). Portals to frailty? Data-driven analyses detect early frailty profiles. *Alzheimer's Research & Therapy*, *13*(1), 1–12. https://doi.org/https://doi.org/10.1186/s13195-020-00736-w

Borelli, W. V., Carmona, K. C., Studart-Neto, A., Nitrini, R., Caramelli, P., & da Costa, J. C. (2018). Operationalized definition of older adults with high cognitive performance. *Dementia e Neuropsychologia*, *12*(3), 221–227. https://doi.org/10.1590/1980-57642018dn12-030001

Borges, M. K., Canevelli, M., Cesari, M., & Aprahamian, I. (2019a). Frailty as a predictor of cognitive disorders: A systematic review and meta-analysis. *Frontiers in Medicine*, *6*(26), 1–8. https://doi.org/10.3389/fmed.2019.00026

Borges, M. K., Oiring de Castro Cezar, N., Silva Santos Siqueira, A., Yassuda, M., Cesari, M., & Aprahamian, I. (2019b). The relationship between physical frailty and mild cognitive impairment in the elderly: A systematic review. *The Journal of Frailty & Aging*, *8*(4), 192–197. https://doi.org/10.14283/jfa.2019.29

Bott, N. T., Bettcher, B. M., Yokoyama, J. S., Frazier, D. T., Wynn, M., Karydas, A., Yaffe, K., & Kramer, J. H. (2017). Youthful processing speed in older adults: Genetic, biological, and behavioral predictors of cognitive processing speed trajectories in aging. *Frontiers in Aging Neuroscience*, *9*(55), 1–9. https://doi.org/10.3389/fnagi.2017.00055

Boyle, P., Buchman, A. S., Wilson, R. S., Leurgans, S. E., & Bennett, D. A. (2010). Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *Journal of the American Geriatrics Society*, *58*(2), 248–255. https://doi.org/doi:10.1111/j.1532-5415.2009.02671.x

Bray, B. C., Lanza, S. T., & Tan, X. (2015). Eliminating bias in classify-analyze approaches for latent class analysis. *Structural Equation Modeling*, *22*(1), 1–11. https://doi.org/10.1080/10705511.2014.935265

Bray, G. M., & Huggett, D. L. (2016). Neurological diseases, disorders and injuries in Canada: Highlights of a national study. *Canadian Journal of Neurological Sciences*, *43*(1), 5–14. https://doi.org/10.1017/cjn.2015.312

Brigola, A. G., Rossetti, E. S., Rodrigues, B., Neri, A. L., Zazzetta, M. S., Inouye, K., Cristina, S., Pavarini, I., Santos, B. R. Dos, Neri, A. L., Zazzetta, M. S., Inouye, K., & Pavarini, S. C. I. (2015). Relationship between cognition and frailty in elderly: A systematic review. *Dementia & Neuropsychologia*, *9*(2), 110–119. https://doi.org/10.1590/1980-57642015DN92000005

Brown, P. J., Devanand, D. P., Liu, X., & Caccappolo, E. (2011). Functional impairment in elderly patients with mild cognitive impairment and mild Alzheimer disease. *Archives of General Psychiatry*, *68*(6), 617–626. https://doi.org/10.1001/archgenpsychiatry.2011.57

Buchman, A. S., Boyle, P. A., Wilson, R. S., Tang, Y., & Bennett, D. A. (2007). Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosomatic Medicine*, *69*(5), 483–489. https://doi.org/10.1097/psy.0b013e318068de1d

Buchman, A. S., Schneider, J. A., Leurgans, S., & Bennett, D. A. (2008). Physical frailty in older persons is associated with Alzheimer disease pathology. *Neurology*, *71*(7), 499–504. https://doi.org/10.1212/01.wnl.0000324864.81179.6a

Buchman, A. S., Yu, L., Wilson, R. S., Boyle, P. A., Schneider, J. A., & Bennett, D. A. (2014). Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *69*(12), 1536–1544. https://doi.org/10.1093/gerona/glu117

Buchman, A. S., Yu, L., Wilson, R. S., Schneider, J. A., & Bennett, D. A. (2013). Association of brain pathology with the progression of frailty in older adults. *Neurology*, *80*(22), 2055–2061. https://doi.org/10.1212/WNL.0b013e318294b462

Bunce, D., Batterham, P. J., & Mackinnon, A. J. (2019). Long-term associations between physical frailty and performance in specific cognitive domains. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *74*(6), 919–926. https://doi.org/10.1093/geronb/gbx177

Burt, J. R., Godin, J., Filion, J., Montero-odasso, M., Rockwood, K., Andrew, M. K., & Camicioli, R. (2019). Frailty prevalence in the COMPASS-ND study of neurodegenerative disorders. *Canadian Geriatrics Journal*, *22*(4), 205–212. https://doi.org/https://doi.org/10.5770/cgj.22.392

Buta, B., Walson, J. D., Godino, J. G., Park, M., Kalyani, R. R., Xue, Q. L., Bandeen-Roche, K., & Varadhan, R. (2016). Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Research Reviews*, *26*, 53–61. https://doi.org/10.1016/j.arr.2015.12.003

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 183–213.

Caballero, H. S., McFall, G. P., Wiebe, S. A., & Dixon, R. A. (2020). Integrating three characteristics of executive function in non-demented aging: Trajectories, classification, and biomarker predictors. *Journal of the International Neuropsychological Society*, 1–14. https://doi.org/10.1017/S1355617720000703

Caballero, H. S., McFall, G. P., Zheng, Y., Dixon, R. A. (2021), Data-driven approaches to executive function performance and structure in aging: Integrating person-centered analyses and machine learning risk prediction. *Neuropsychology*, *35*(8), 889-903. https://doi.org/10.1037/neu0000775

Canevelli, M., Bruno, G., Remiddi, F., Vico, C., Lacorte, E., Vanacore, N., & Cesari, M. (2017). Spontaneous reversion of clinical conditions measuring the risk profile of the individual: From frailty to mild cognitive impairment. *Frontiers in Medicine*, *4*(184), 1–6. https://doi.org/10.3389/fmed.2017.00184

Canevelli, M., Cesari, M., & van Kan, G. A. (2015). Frailty and cognitive decline: How do they relate? *Current Opinion in Clinical Nutrition and Metabolic Care*, *18*(1), 43–50. https://doi.org/10.1097/MCO.0000000000000133

Cardoso, A. L., Fernandes, A., Aguilar-Pimentel, J. A., de Angelis, M. H., Guedes, J. R., Brito, M. A., Ortolano, S., Pani, G., Athanasopoulou, S., Gonos, E. S., Schosserer, M., Grillari, J., Peterson, P., Tuna, B. G., Dogan, S., Meyer, A., van Os, R., & Trendelenburg, A. U. (2018). Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. *Ageing Research Reviews*, *47*, 214–277. https://doi.org/10.1016/j.arr.2018.07.004

Cesari, M., Gambassi, G., van Kan, G. A., & Vellas, B. (2014). The frailty phenotype and the frailty index: Different instruments for different purposes. *Age and Ageing*, *43*(1), 10–12. https://doi.org/10.1093/ageing/aft160

Chang, W. C., Lu, F. P., Lan, T. Y., & Wu, S. C. (2013). Multidimensional health-transition patterns among a middle-aged and older population. *Geriatrics and Gerontology International*, *13*(3), 571–579. https://doi.org/10.1111/j.1447-0594.2012.00937.x

Chen, F., Bollen, K. A., Paxton, P., Curran, P. J., & Kirby, J. B. (2001). Improper solutions in structural equation models: Causes, consequences, and strategies. *Sociological Methods & Research*, *29*(4), 468–508. https://doi.org/10.1177/0049124101029004003

Cheng, C. M., Chang, W. H., Chiu, Y. C., Sun, Y., Lee, H. J., Tang, L. Y., Wang, P. N., Chiu, M. J., Yang, C. H., Tsai, S. J., & Tsai, C. F. (2018). Association of polypharmacy with mild cognitive impairment and cognitive ability: A nationwide survey in Taiwan. *Journal of Clinical Psychiatry*, *79*(6), e1–e8. https://doi.org/10.4088/JCP.17m12043

Chertkow, H., Borrie, M., Whitehead, V., Black, S. E., Feldman, H. H., Gauthier, S., Hogan, D. B., Masellis, M., McGilton, K., Rockwood, K., Tierney, M. C., Andrew, M., Hsiung, G. Y. R., Camicioli, R., Smith, E. E., Fogarty, J., Lindsay, J., Best, S., Evans, A., … Rylett, R. J. (2019). The Comprehensive Assessment of Neurodegeneration and Dementia: Canadian cohort study. *Canadian Journal of Neurological Sciences*, *46*(5), 499–511. https://doi.org/10.1017/cjn.2019.27

Chhetri, J. K., Chan, P., Vellas, B., & Cesari, M. (2017). Motoric cognitive risk syndrome: Predictor of dementia and age-related negative outcomes. *Frontiers in Medicine*, *4*(166), 1–8. https://doi.org/10.3389/fmed.2017.00166

Chong, M. S., Tay, L., Chan, M., Lim, W. S., Ye, R., Tan, E. K., & Ding, Y. Y. (2015). Prospective longitudinal study of frailty transitions in a community-dwelling cohort of older adults with cognitive impairment. *BMC Geriatrics*, *15*(175), 1–12. https://doi.org/10.1186/s12877-015-0174-1

Clark, S., & Muthén, B. O. (2009). *Relating latent class analysis results to variables not included in the analysis.* http://www.statmodel. com/download/relatinglca.pdf

Clegg, A., Young, J., Iliffe, S., Olde Rikkert, M. G. M., & Rockwood, K. (2013). Frailty in older people. *Lancet*, *381*(9868), 752–762. https://doi.org/10.1016/S0140-6736(12)62167-9

Cloutier, S., Chertkow, H., Kergoat, M. J., Gélinas, I., Gauthier, S., & Belleville, S. (2021). Trajectories of decline on instrumental activities of daily living prior to dementia in persons with mild cognitive impairment. *International Journal of Geriatric Psychiatry*, *36*(2), 314–323. https://doi.org/10.1002/gps.5426

Collard, R. M., Boter, H., Schoevers, R. A., & Oude Voshaar, R. C. (2012). Prevalence of frailty in community-dwelling older persons: A systematic review. *Journal of the American Geriatrics Society*, *60*(8), 1487–1492. https://doi.org/10.1111/j.1532-5415.2012.04054.x

Collins, L. M., & Lanza, S. T. (2010). *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences*. John Wiley & Sons, Inc.

Connell, A., Bullock, B. M., Dishion, T. J., Shaw, D., Wilson, M., & Gardner, F. (2008). Family intervention effects on co-occurring early childhood behavioral and emotional problems: A latent transition analysis approach. *Journal of Abnormal Child Psychology*, *36*(8), 1211–1225. https://doi.org/10.1007/s10802-008-9244-6

Cooper, C., Sommerlad, A., Lyketsos, C. G., & Livingston, G. (2015). Modifiable predictors of dementia in mild cognitive impairment: A systematic review and meta-analysis. *American Journal of Psychiatry*, *172*(4), 323–334. https://doi.org/10.1176/appi.ajp.2014.14070878

Costello, A. B., & Osborne, J. W. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research & Evaluation*, *10*(7), 1–9. https://doi.org/10.7275/jyj1-4868

Cui, M., Zhang, S., Liu, Y., Gang, X., & Wang, G. (2021). Grip strength and the risk of cognitive decline and dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Frontiers in Aging Neuroscience*, *13*(625551), 1–11. https://doi.org/10.3389/fnagi.2021.625551

Cummings, J. L. (1997). The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*, *48*(s6), S10–S16. https://doi.org/10.1212/wnl.48.5_suppl_6.10s

Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimer's Research and Therapy*, *6*(37), 1–7. https://doi.org/10.1186/alzrt269

Cummings, J., Lee, G., Ritter, A., Sabbagh, M., & Zhong, K. (2019). Alzheimer's disease drug development pipeline: 2019. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *5*, 272–293. https://doi.org/10.1016/j.trci.2019.05.008

de Frias, C. M., Dixon, R. A., & Strauss, E. (2009). Characterizing executive functioning in older special populations: From cognitively elite to cognitively impaired. *Neuropsychology*, *23*(6), 778–791. https://doi.org/doi:10.1037/a0016743

de Moraes e Silva, M., Mercer, P. B. S., Witt, M. C. Z., & Pessoa, R. R. (2018). Olfactory dysfunction in Alzheimer's disease: Systematic review and meta-analysis. *Dementia e Neuropsychologia*, *12*(2), 123–132. https://doi.org/10.1590/1980-57642018dn12-020004

Dimitriadis, S. I., Liparas, D., & Tsolaki, M. N. (2018). Random forest feature selection, fusion and ensemble strategy: Combining multiple morphological MRI measures to discriminate among healthy elderly, MCI, cMCI and Alzheimer's disease patients: From the Alzheimer's Disease Neuroimaging Initiative (ADNI) data. *Journal of Neuroscience Methods*, *302*, 14–23. https://doi.org/10.1016/j.jneumeth.2017.12.010

Dixon, R. A., & de Frias, C. M. (2004). The Victoria Longitudinal Study: From characterizing cognitive aging to illustrating changes in memory compensation. *Aging, Neuropsychology, and Cognition*, *11*(2), 346–376. https://doi.org/https://doi.org/10.1080/13825580490511161

Dixon, R. A., & de Frias, C. M. (2014). Cognitively elite, cognitively normal, and cognitively impaired aging: Neurocognitive status and stability moderate memory performance. *Journal of Clinical and Experimental Neuropsychology*, *36*(4), 418–430. https://doi.org/10.1080/13803395.2014.903901

Dixon, R. A., & Lachman, M. E. (2019). Risk and protective factors in cognitive aging: Advances in assessment, prevention, and promotion of alternative pathways. In G. Samanez-larkin (Ed.), *The Aging Brain: Functional Adaptation Across Adulthood* (pp. 217–263). American Psychological Association.

Dodd, J. W. (2015). Lung disease as a determinant of cognitive decline and dementia. *Alzheimer's Research and Therapy*, *7*(32), 1–8. https://doi.org/10.1186/s13195-015-0116-3

Doi, T., Makizako, H., Tsutsumimoto, K., Nakakubo, S., Kim, M. J., Kurita, S., Hotta, R., & Shimada, H. (2018). Transitional status and modifiable risk of frailty in Japanese older adults:

A prospective cohort study. *Geriatrics & Gerontology International*, *18*(11), 1562–1566. https://doi.org/10.1111/ggi.13525

Dolcos, S., MacDonald, S. W. S., Braslavsky, A., Camicioli, R., & Dixon, R. A. (2012). Mild cognitive impairment is associated with selected functional markers: Integrating concurrent, longitudinal, and stability effects. *Neuropsychology*, *26*(2), 209–223. https://doi.org/10.1037/a0026760

Dong, X., Nao, J., Shi, J., & Zheng, D. (2019). Predictive value of routine peripheral blood biomarkers in Alzheimer's disease. *Frontiers in Aging Neuroscience*, *11*(332), 1–9. https://doi.org/10.3389/fnagi.2019.00332

Drouin, S. M., McFall, G. P., & Dixon, R. A. (2020). In multiple facets of subjective memory decline sex moderates memory predictions. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *12*(e12089), 1–8. https://doi.org/10.1002/dad2.12089

Dubal, D. B. (2020). Sex difference in Alzheimer's disease: An updated, balanced and emerging perspective on differing vulnerabilities. In G. S. K. & I. S. R. Lanzenberger (Eds.), *Handbook of clinical neurology* (3rd series, Vol. 175, pp. 261–273). Elsevier B.V. https://doi.org/10.1016/B978-0-444-64123-6.00018-7

Duggan, E. C., Graham, R. B., Piccinin, A. M., Jenkins, N. D., Clouston, S., Muniz-Terrera, G., & Hofer, S. M. (2018). Systematic review of pulmonary function and cognition in aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *75*(5), 937-952. https://doi.org/10.1093/geronb/gby128

Eckert, M. A., Keren, N. I., Roberts, D. R., Calhoun, V. D., & Harris, K. C. (2010). Age-related changes in processing speed: Unique contributions of cerebellar and prefrontal cortex. *Frontiers in Human Neuroscience*, *4*(10), 1–14. https://doi.org/10.3389/neuro.09.010.2010

Enders, C. K. (2011). Analyzing longitudinal data with missing values. *Rehabilitation Psychology*, *56*(4), 267-288. doi: 10.1037/a0025579

Etman, A., Burdorf, A., van der Cammen, T. J. M., Mackenbach, J. P., & van Lenthe, F. J. (2012). Socio-demographic determinants of worsening in frailty among community-dwelling older people in 11 European countries. *Journal of Epidemiology and Community Health*, *66*(12), 1116–1121. https://doi.org/10.1136/jech-2011-200027

Fabrício, D. de M., Chagas, M. H. N., & Diniz, B. S. (2020). Frailty and cognitive decline. *Translational Research*, *221*, 58–64. https://doi.org/10.1016/j.trsl.2020.01.002

Fallah, N., Mitnitski, A., Searle, S. D., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2011). Transitions in frailty status in older adults in relation to mobility: A multistate modeling approach employing a deficit count. *Journal of the American Geriatrics Society*, *59*(3), 524–529. https://doi.org/10.1111/j.1532-5415.2011.03300.x

Fernández-Garrido, J., Ruiz-Ros, V., Buigues, C., Navarro-Martinez, R., & Cauli, O. (2014). Clinical features of prefrail older individuals and emerging peripheral biomarkers: A systematic review. *Archives of Gerontology and Geriatrics*, *59*(1), 7–17. https://doi.org/10.1016/j.archger.2014.02.008

Fischer, M. E., Cruickshanks, K. J., Schubert, C. R., Pinto, A. A., Carlsson, C. M., Klein, B. E. K., Klein, R., & Tweed, T. S. (2016). Age-related sensory impairments and risk of cognitive impairment. *Journal of the American Geriatrics Society*, *64*(10), 1981–1987. https://doi.org/10.1111/jgs.14308

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S. G., Krampla, W., & Tragl, K. H. (2007). Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology*, *68*(4), 288–291. https://doi.org/10.1212/01.wnl.0000278072.42014.6d

Folstein, M. F., & Folstein, S. E. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fonseca, J. A. S., Ducksbury, R., Rodda, J., Whitfield, T., Nagaraj, C., Suresh, K., Stevens, T., & Walker, Z. (2015). Factors that predict cognitive decline in patients with subjective cognitive impairment. *International Psychogeriatrics*, *27*(10), 1671–1677. https://doi.org/10.1017/S1041610215000356

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., Burke, G., & McBurnie, M. A. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(3), M146–M156. https://doi.org/10.1093/gerona/56.3.M146

Fulop, T., Larbi, A., Witkowski, J. M., McElhaney, J., Loeb, M., Mitnitski, A., & Pawelec, G. (2010). Aging, frailty and age-related diseases. *Biogerontology*, *11*(5), 547–563. https://doi.org/10.1007/s10522-010-9287-2

Galbraith, S., Bowden, J., & Mander, A. (2017). Accelerated longitudinal designs: An overview of modelling, power, costs and handling missing data. *Statistical Methods in Medical Research*, *26*(1), 374–398. https://doi.org/10.1177/0962280214547150

Gallucci, A., Trimarchi, P. D., Abbate, C., Tuena, C., Pedroli, E., Lattanzio, F., Stramba-Badiale, M., Cesari, M., & Giunco, F. (2020). ICT technologies as new promising tools for the managing of frailty: A systematic review. *Aging Clinical and Experimental Research*, *33*(6), 1453–1464. https://doi.org/10.1007/s40520-020-01626-9

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: An epidemiologic study. *Neurology*, *63*(1), 115–121. https://doi.org/10.1212/01.WNL.0000132523.27540.81

Garre-Olmo, J., Calvó-Perxas, L., López-Pousa, S., De Gracia Blanco, M., & Vilalta-Franch, J. (2013). Prevalence of frailty phenotypes and risk of mortality in a community-dwelling elderly cohort. *Age and Ageing*, *42*(1), 46–51. https://doi.org/10.1093/ageing/afs047

Ghorbani, A., & Zou, J. (2019). Data Shapley: Equitable valuation of data for machine learning. *Proceedings of the 36th International Conference on Machine Learning*, 97, 2242–2251. arXiv:1904.02868

Gifford, K. A., Bell, S. P., Liu, D., Neal, J. E., Turchan, M., Shah, A. S., & Jefferson, A. L. (2019). Frailty is related to subjective cognitive decline in older women without dementia. *Journal of the American Geriatrics Society*, *67*(9), 1803–1811. https://doi.org/10.1111/jgs.15972

Gobbens, R. J. J., van Assen, M. A. L. M., Luijkx, K. G., Wijnen-Sponselee, M. T., & Schols, J. M. G. A. (2010). The Tilburg Frailty Indicator: Psychometric properties. *Journal of the American Medical Directors Association*, *11*(5), 344–355. https://doi.org/10.1016/j.jamda.2009.11.003

Godin, J., Armstrong, J. J., Rockwood, K., & Andrew, M. K. (2017). Dynamics of frailty and cognition after age 50: Why it matters that cognitive decline is mostly seen in old age. *Journal of Alzheimer's Disease*, *58*(1), 231–242. https://doi.org/10.3233/JAD-161280

Gómez-Ramírez, J., Ávila-Villanueva, M., & Fernández-Blázquez, M. Á. (2020). Selecting the most important self-assessed features for predicting conversion to mild cognitive impairment with random forest and permutation-based methods. *Scientific Reports*, *10*(1), 1–15. https://doi.org/10.1038/s41598-020-77296-4

Gonzalez-Colaço Harmand, M., Meillon, C., Bergua, V., Tabue Teguo, M., Dartigues, J. F., Avila-Funes, J. A., & Amieva, H. (2017). Comparing the predictive value of three definitions of frailty: Results from the Three-City Study. *Archives of Gerontology and Geriatrics*, *72*, 153–163. https://doi.org/10.1016/j.archger.2017.06.005

Goonawardene, N., Tan, H. P., & Tan L. B. (2018) Unobtrusive detection of frailty in older adults. In J. Zhou & G. Salvendy (Eds., vol 10927), *Human Aspects of IT for the Aged Population. Applications in Health, Assistance, and Entertainment*. *ITAP 2018*. Lecture Notes in Computer Science. Springer, Cham. https://doi.org/10.1007/978-3-319-92037-5_22

Gordon, E. H., Peel, N. M., Samanta, M., Theou, O., Howlett, S. E., & Hubbard, R. E. (2017). Sex differences in frailty: A systematic review and meta-analysis. *Experimental Gerontology*, *89*, 30–40. https://doi.org/10.1016/j.exger.2016.12.021

Grande, G., Haaksma, M. L., Rizzuto, D., Melis, R. J. F., Marengoni, A., Onder, G., Welmer, A. K., Fratiglioni, L., & Vetrano, D. L. (2019). Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: Systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *107*, 96–103. https://doi.org/10.1016/j.neubiorev.2019.09.001

Gray, S. L., Anderson, M. L., Hubbard, R. A., Lacroix, A., Crane, P. K., McCormick, W., Bowen, J. D., McCurry, S. M., & Larson, E. B. (2013). Frailty and incident dementia. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *68*(9), 1083–1090. https://doi.org/10.1093/gerona/glt013

Greene, B. R., Doheny, E. P., Kenny, R. A., & Caulfield, B. (2014). Classification of frailty and falls history using a combination of sensor-based mobility assessments. *Physiological Measurement*, *35*(10), 2053-2066. doi: 10.1088/0967-3334/35/10/2053

Halil, M., Kizilarslanoglu, C. M., Emin Kuyumcu, M., Yesil, Y., & Cruz Jentoft, A. J. (2015). Cognitive aspects of frailty: Mechanisms behind the link between frailty and cognitive impairment. *Journal of Nutrition, Health and Aging*, *19*(3), 276–283. https://doi.org/10.1007/s12603-014-0535-z

Hao, L., Xing, Y., Li, X., Mu, B., Zhao, W., Wang, G., Wang, T., Jia, J., & Han, Y. (2019). Risk factors and neuropsychological assessments of subjective cognitive decline (plus) in Chinese memory clinic. *Frontiers in Neuroscience*, *13*(846), 1–11. https://doi.org/10.3389/fnins.2019.00846

Harada, C. N., Natelson Love, M. C., & Triebel, K. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002

Hassler, A. P., Menasalvas, E., García-García, F. J., Rodríguez-Mañas, L., & Holzinger, A. (2019). Importance of medical data preprocessing in predictive modeling and risk factor discovery for the frailty syndrome. *BMC Medical Informatics and Decision Making*, *19*(33), 1–17. https://doi.org/10.1186/s12911-019-0747-6

Hastie, T., Tibshirani, R., & Friedman, J. (2009). *The Elements of Statistical Learning: Data Mining, Inference, and Prediction* (2nd ed.). Springer.

Hayden, K. M., Reed, B. R., Manly, J. J., Tommet, D., Pietrzak, R. H., Chelune, G. J., Yang, F. M., Revell, A. J., Bennett, D. A., & Jones, R. N. (2011). Cognitive decline in the elderly: An analysis of population heterogeneity. *Age and Ageing*, *40*(6), 684–689. https://doi.org/10.1093/ageing/afr101

Heikkilä, E., Salminen, M., Viljanen, A., Katajamäki, T., Koivula, M. K., Pulkki, K., Isoaho, R., Kivelä, S. L., Viitanen, M., Löppönen, M., Vahlberg, T., Viikari, L., & Irjala, K. (2021). A practical laboratory index to predict institutionalization and mortality– an 18-year population-

based follow-up study. *BMC Geriatrics*, *21*(139), 1–6. https://doi.org/10.1186/s12877-021-02077-1

Hill, N. L., McDermott, C., Mogle, J., Munoz, E., Depasquale, N., Wion, R., & Whitaker, E. (2017). Subjective cognitive impairment and quality of life: A systematic review. *International Psychogeriatrics*, *29*(12), 1965–1977. https://doi.org/10.1017/S1041610217001636

Hill, N. L., Mogle, J., Wion, R., Munoz, E., DePasquale, N., Yevchak, A. M., & Parisi, J. M. (2016). Subjective cognitive impairment and affective symptoms: A systematic review. *Gerontologist*, *56*(6), e109–e127. https://doi.org/10.1093/geront/gnw091

Hochstetler, H., Trzepacz, P. T., Wang, S., Yu, P., Case, M., Henley, D. B., Degenhardt, E., Leoutsakos, J. M., & Lyketsos, C. G. (2016). Empirically defining trajectories of late-life cognitive and functional decline. *Journal of Alzheimer's Disease*, *50*(1), 271–282. https://doi.org/10.3233/JAD-150563

Hooghiemstra, A. M., Ramakers, I. H. G. B., Sistermans, N., Pijnenburg, Y. A. L., Aalten, P., Hamel, R. E. G., Melis, R. J. F., Verhey, F. R. J., Olde Rikkert, M. G. M., Scheltens, P., & van der Flier, W. M. (2017). Gait speed and grip strength reflect cognitive impairment and are modestly related to incident cognitive decline in memory clinic patients with subjective cognitive decline and mild cognitive impairment: Findings from the 4C study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *72*(6), 846–854. https://doi.org/10.1093/gerona/glx003

Howlett, S. E., Rockwood, M. R. H., Mitnitski, A., & Rockwood, K. (2014). Standard laboratory tests to identify older adults at increased risk of death. *BMC Medicine*, *12*(171), 1–8. https://doi.org/10.1016/j.jalz.2015.06.975

Hsieh, T., Chang, H., Wu, I., Chen, C., Tsai, H., Chiu, F., Chuang, S., Hsiung, C. A., & Hsu, C. (2018). Independent association between subjective cognitive decline and frailty in the elderly. *PLoS ONE*, *18*(8), 1–12. https://doi.org/10.1371/journal.pone.0201351

Hubbard, R. E. (2015). Sex differences in frailty. *Interdisciplinary Topics in Gerontology and Geriatrics*, *41*, 41–53. https://doi.org/10.1159/000381161

Hubbard, R. E., & Rockwood, K. (2011). Frailty in older women. *Maturitas*, *69*(3), 203–207. https://doi.org/10.1016/j.maturitas.2011.04.006

Hyde, Z., Smith, K., Flicker, L., Atkinson, D., Fenner, S., Skeaf, L., Malay, R., & lo Giudice, D. (2019). HbA1c Is Associated with frailty in a group of Aboriginal Australians. *The Journal of Frailty & Aging*, *8*(1), 17–20. https://doi.org/10.14283/jfa.2018.41

Inzitari, M., Newman, A. B., Yaffe, K., Boudreau, R., De Rekeneire, N., Shorr, R., Harris, T. B., & Rosano, C. (2007). Gait speed predicts decline in attention and psychomotor speed in older adults: The Health Aging and Body Composition study. *Neuroepidemiology*, *29*(3-4), 156–162. https://doi.org/10.1159/000111577

Jack, C. R., Therneau, T. M., Weigand, S. D., Wiste, H. J., Knopman, D. S., Vemuri, P., Lowe, V. J., Mielke, M. M., Roberts, R. O., Machulda, M. M., Graff-Radford, J., Jones, D. T., Schwarz, C. G., Gunter, J. L., Senjem, M. L., Rocca, W. A., & Petersen, R. C. (2019). Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging-Alzheimer's Association Research Framework. *JAMA Neurology*, *76*(10), 1174–1183. https://doi.org/10.1001/jamaneurol.2019.1971

Janoutová, J., Šerý, O., Hosák, L., & Janout, V. (2015). Is mild cognitive impairment a precursor of Alzheimer's disease? Short review. *Central European Journal of Public Health*, *23*(4), 365–367. https://doi.org/10.21101/cejph.a4414

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., Dubois, B., Eriksdotter, M., Ewers, M., Graessel, E., Kramberger, M. G., Law, E., Mecocci, P., Molinuevo, J. L., Nygård, L., Olde-Rikkert, M. G., Orgogozo, J. M., Pasquier, F., Peres, K., … Frölich, L. (2015). Mild cognitive impairment and deficits in instrumental activities of daily living: A systematic review. *Alzheimer's Research & Therapy*, *7*(1), 1–20. https://doi.org/10.1186/s13195-015-0099-0

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K. A., van der Flier, W. M., Glodzik, L., van Harten, A. C., de Leon, M. J., McHugh, P., Mielke, M. M., Molinuevo, J. L., Mosconi, L., Osorio, R. S., Perrotin, A., … Wagner, M. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's and Dementia*, *10*(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001

Josefsson, M., De Luna, X., Pudas, S., Nilsson, L. G., & Nyberg, L. (2012). Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *Journal of the American Geriatrics Society*, *60*(12), 2308–2312. https://doi.org/10.1111/jgs.12000

Jung, H. J., Shin, I. S., & Lee, J. E. (2019). Olfactory function in mild cognitive impairment and Alzheimer's disease: A meta-analysis. *Laryngoscope*, *129*(2), 362–369. https://doi.org/10.1002/lary.27399

Jutten, R. J., Dicks, E., Vermaat, L., Barkhof, F., Scheltens, P., Tijms, B. M., & Sikkes, S. A. M. (2019). Impairment in complex activities of daily living is related to neurodegeneration in Alzheimer's disease–specific regions. *Neurobiology of Aging*, *75*, 109–116. https://doi.org/10.1016/j.neurobiolaging.2018.11.018

Kamaruzzaman, S., Ploubidis, G. B., Fletcher, A., & Ebrahim, S. (2010). A reliable measure of frailty for a community dwelling older population. *Health and Quality of Life Outcomes*, *8*(123), 1–14. https://doi.org/10.1186/1477-7525-8-123

Kang, Y. J., Yoo, J. Il, & Ha, Y. C. (2019). Sarcopenia feature selection and risk prediction using machine learning: A cross-sectional study. *Medicine*, *98*(43), 1–8. https://doi.org/10.1097/MD.0000000000017699

Kim, J., Angel, J. L., & Rote, S. M. (2021). A longitudinal study of cognitive and instrumental activities of daily living disablement among the oldest Mexican Americans. *Journal of Aging and Health*. https://doi.org/10.1177/08982643211037512

Kim, Y. J., Cho, S. K., Kim, H. J., Lee, J. S., Lee, J., Jang, Y. K., Vogel, J. W., Na, D. L., Kim, C., & Seo, S. W. (2019). Data-driven prognostic features of cognitive trajectories in patients with amnestic mild cognitive impairments. *Alzheimer's Research and Therapy*, *11*(1), 1–9. https://doi.org/10.1186/s13195-018-0462-z

Kojima, G. (2015). Prevalence of frailty in nursing homes: A systematic review and meta-analysis. *Journal of the American Medical Directors Association*, *16*(11), 940–945. https://doi.org/10.1016/j.jamda.2015.06.025

Kojima, G., A., L., Iliffe, S., & Walters, K. (2017). Prevalence of frailty in mild to moderate Alzheimer's disease: A systematic review and meta-analysis. *Current Alzheimer Research*, *14*(12), 1256–1263. https://doi.org/10.2174/1567205014666170417104236

Kojima, G., Taniguchi, Y., Iliffe, S., Jivraj, S., & Walters, K. (2019). Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis. *Ageing Research Reviews*, *50*, 81–88. https://doi.org/10.1016/j.arr.2019.01.010

Kontis, V., Bennett, J. E., Mathers, C. D., Li, G., Foreman, K., & Ezzati, M. (2017). Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet*, *389*(10076), 1323–1335. https://doi.org/10.1016/S0140-6736(16)32381-9

Koppara, A., Wagner, M., Lange, C., Ernst, A., Wiese, B., König, H. H., Brettschneider, C., Riedel-Heller, S., Luppa, M., Weyerer, S., Werle, J., Bickel, H., Mösch, E., Pentzek, M., Fuchs, A., Wolfsgruber, S., Beauducel, A., Scherer, M., Maier, W., & Jessen, F. (2015). Cognitive performance before and after the onset of subjective cognitive decline in old age. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *1*(2), 194–205. https://doi.org/10.1016/j.dadm.2015.02.005

Kruse, C., Goemaere, S., De Buyser, S., Lapauw, B., Eiken, P., & Vestergaard, P. (2018). Predicting mortality and incident immobility in older Belgian men by characteristics related to sarcopenia and frailty. *Osteoporosis International*, *29*(6), 1437–1445. https://doi.org/10.1007/s00198-018-4467-z

Kuhn, M., & Johnson, K. (2013). *Applied predictive modeling*. Springer.

Kulminski, A. M., Ukraintseva, S. v., Kulminskaya, I. v., Arbeev, K. G., Land, K., & Yashin, A. I. (2008). Cumulative deficits better characterize susceptibility to death in elderly people than phenotypic frailty: Lessons from the Cardiovascular Health Study. *Journal of the American Geriatrics Society*, *56*(5), 898–903. https://doi.org/10.1111/j.1532-5415.2008.01656.x

Kulminski, A., Ukraintseva, S. v., Arbeev, K. G., Manton, K. G., Oshima, J., Martin, G. M., & Yashin, A. I. (2008). Association between APOE ε2/ε3/ε4 polymorphism and disability severity in a national long-term care survey sample. *Age and Ageing*, *37*(3), 288–293. https://doi.org/10.1093/ageing/afn003

Lacas, A., & Rockwood, K. (2012). Frailty in primary care: A review of its conceptualization and implications for practice. *BMC Medicine*, *10*(4), 1–9. https://doi.org/http://www.biomedcentral.com/1741-7015/10/4

Lafortune, L., Béland, F., Bergman, H., & Ankri, J. (2009). Health status transitions in community-living elderly with complex care needs: A latent class approach. *BMC Geriatrics*, *9*(6), 1–14. https://doi.org/10.1186/1471-2318-9-6

Landeiro, F., Mughal, S., Walsh, K., Nye, E., Morton, J., Williams, H., Ghinai, I., Castro, Y., Leal, J., Roberts, N., Wace, H., Handels, R., Lecomte, P., Gustavsson, A., Roncancio-Diaz, E., Belger, M., Jhuti, G. S., Bouvy, J. C., Potashman, M. H., … Gray, A. M. (2020). Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: A systematic literature review. *Alzheimer's Research & Therapy*, *12*(154), 1–14. https://doi.org/10.1186/s13195-020-00723-1

Langeard, A., Pothier, K., Morello, R., Lelong-Boulouard, V., Lescure, P., Bocca, M. L., Marcelli, C., Descatoire, P., & Chavoix, C. (2016). Polypharmacy cut-off for gait and cognitive impairments. *Frontiers in Pharmacology*, *7*(296), 1–6. https://doi.org/10.3389/fphar.2016.00296

Lanza, S. T., & Collins, L. M. (2008). A new SAS procedure for latent transition analysis: Transitions in dating and sexual risk behavior. *Developmental Psychology*, *44*(2), 446–456. https://doi.org/10.1037/0012-1649.44.2.446

Lanza, S. T., Patrick, M. E., & Maggs, J. L. (2010). Latent transition analysis: Benefits of a latent variable approach to modeling transitions in substance use. *Journal of Drug Issues*, *40*(1), 93–120. https://doi.org/10.1177/002204261004000106

Lara, J., Cooper, R., Nissan, J., Ginty, A. T., Khaw, K. T., Deary, I. J., Lord, J. M., Kuh, D., & Mathers, J. C. (2015). A proposed panel of biomarkers of healthy ageing. *BMC Medicine*, *13*(222), 1–8. https://doi.org/10.1186/s12916-015-0470-9

Laudisio, A., Navarini, L., Margiotta, D. P. E., Fontana, D. O., Chiarella, I., Spitaleri, D., Bandinelli, S., Gemma, A., Ferrucci, L., & Incalzi, R. A. (2019). The association of olfactory dysfunction, frailty, and mortality is mediated by inflammation: Results from the InCHIANTI study. *Journal of Immunology Research*, *2019*, 1–8. https://doi.org/10.1155/2019/3128231

Lee, J. S. W., Auyeung, T. W., Leung, J., Kwok, T., & Woo, J. (2014). Transitions in frailty states among community-living older adults and their associated factors. *Journal of the American Medical Directors Association*, *15*(4), 281–286. https://doi.org/10.1016/j.jamda.2013.12.002

Leelakanok, N., & D'Cunha, R. R. (2019). Association between polypharmacy and dementia– A systematic review and metaanalysis. *Aging and Mental Health*, *23*(8), 932–941. https://doi.org/10.1080/13607863.2018.1468411

Liang, J., Xu, X., Bennett, J. M., Ye, W., & Quiñones, A. R. (2009). Ethnicity and changing functional health in middle and late life: A person-centered approach. *Journal of Gerontology: Social Sciences*, *65B*(4), 474-481. doi:10.1093/geronb/gbp114

Lim, W.-S., Canevelli, M., & Cesari, M. (2018). Editorial: Dementia, frailty and aging. *Frontiers in Medicine*, *5*(168), 1–3. https://doi.org/10.3389/fmed.2018.00168

Lin, F., Chen, D. G., Vance, D., & Mapstone, M. (2013). Trajectories of combined laboratory-and real world-based speed of processing in community-dwelling older adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *68*(3), 364–373. https://doi.org/10.1093/geronb/gbs075

Lin, F., Wang, X., Rebok, G. W., Chapman, B. P., & Initiative, A. D. N. (2017). Identification of successful cognitive aging in the Alzheimer's Disease Neuroimaging Initiative Study. *Journal of Alzheimer's Disease*, *59*(1), 101–111. https://doi.org/10.3233/JAD-161278

Lin, M. Y., Gutierrez, P. R., Stone, K. L., Yaffe, K., Ensrud, K. E., Fink, H. A., Sarkisian, C. A., Coleman, A. L., & Mangione, C. M. (2004). Vision impairment and combined vision and hearing impairment predict cognitive and functional decline in older women. *Journal of the American Geriatrics Society*, *52*(12), 1996–2002. https://doi.org/10.1111/j.1532-5415.2004.52554.x

Little, T. D. (2013). *Longitudinal structural equation modeling*. Guilford Press.

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms, and therapy. *Nature Reviews Neuroscience*, *9*(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

Liu, L. K., Guo, C. Y., Lee, W. J., Chen, L. Y., Hwang, A. C., Lin, M. H., Peng, L. N., Chen, L. K., & Liang, K. Y. (2017). Subtypes of physical frailty: Latent class analysis and associations with clinical characteristics and outcomes. *Scientific Reports*, *7*(46417), 1–9. https://doi.org/10.1038/srep46417

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R.,

Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet Commissions*, *390*(10113), 2673–2734. https://doi.org/10.1016/S0140-6736(17)31363-6

Lohman, M., Dumenci, L., & Mezuk, B. (2014). Sex differences in the construct overlap of frailty and depression: Evidence from the Health and Retirement Study. *Journal of the American Geriatrics Society*, *62*(3), 500–505. https://doi.org/10.1111/jgs.12689

Looman, W. M., Fabbricotti, I. N., Blom, J. W., Jansen, A. P. D., Lutomski, J. E., Metzelthin, S. F., & Huijsman, R. (2018). The frail older person does not exist: Development of frailty profiles with latent class analysis. *BMC Geriatrics*, *18*(84), 1–11. https://doi.org/10.1186/s12877-018-0776-5

Lund, J. L., Kuo, T. M., Brookhart, M. A., Meyer, A. M., Dalton, A. F., Kistler, C. E., Wheeler, S. B., & Lewis, C. L. (2019). Development and validation of a 5-year mortality prediction model using regularized regression and Medicare data. *Pharmacoepidemiology and Drug Safety*, *28*(5), 584–592. https://doi.org/10.1002/pds.4769

Lundberg, S. M., Erion, G., Chen, H., DeGrave, A., Prutkin, J. M., Nair, B., Katz, R., Himmelfarb, J., Bansal, N., & Lee, S. I. (2020). From local explanations to global understanding with explainable AI for trees. *Nature Machine Intelligence*, *2*(1), 56–67. https://doi.org/10.1038/s42256-019-0138-9

Lundberg, S. M., Erion, G. G., & Lee, S. I. (2018). Consistent individualized feature attribution for tree ensembles (pre-print). *ArXiv:1802.03888*, 1–9.

Lundberg, S. M., & Lee, S. I. (2017). A unified approach to interpreting model predictions (pre-print). *ArXiv:1705.07874v2*, 1–10.

Ma, L., Zhang, L., Zhang, Y., Li, Y., Tang, Z., & Chan, P. (2017). Cognitive frailty in China: Results from China comprehensive geriatric assessment study. *Frontiers in Medicine*, *4*(174), 1–6. https://doi.org/10.3389/fmed.2017.00174

MacDonald, S. W. S., Keller, C. J. C., Brewster, P. W. H., & Dixon, R. A. (2018). Contrasting olfaction, vision, and audition as cognitive change and impairment in non-demented older adults. *Neuropsychology*, *32*(4), 450–460. https://doi.org/10.1037/neu0000439

Majnarić, L. T., Bekić, S., Babič, F., Pusztová, Ľ., & Paralič, J. (2020). Cluster analysis of the associations among physical frailty, cognitive impairment and mental disorders. *Medical Science Monitor*, *26*, e924281-12. https://doi.org/10.12659/MSM.924281

Malhotra, C., Chan, A., Matchar, D., Seow, D., Chuo, A., & Do, Y. K. (2013). Diagnostic performance of Short Portable Mental Status Questionnaire for screening dementia among patients attending cognitive assessment clinics in Singapore. *Annals of the Academy of Medicine Singapore*, *42*(7), 315–319.

Mao, H. F., Chang, L. H., Tsai, A. Y. J., Huang, W. N. W., Tang, L. Y., Lee, H. J., Sun, Y., Chen, T. F., Lin, K. N., Wang, P. N., Shyu, Y. I. L., & Chiu, M. J. (2018). Diagnostic accuracy of instrumental activities of daily living for dementia in community-dwelling older adults. *Age and Ageing*, *47*(4), 551–557. https://doi.org/10.1093/ageing/afy021

Margioti, E., Kosmidis, M. H., Yannakoulia, M., Dardiotis, E., Hadjigeorgiou, G., Sakka, P., Ntanasi, E., Vlachos, G. S., & Scarmeas, N. (2020). Exploring the association between subjective cognitive decline and frailty: The Hellenic Longitudinal Investigation of Aging and Diet Study (HELIAD). *Aging and Mental Health*, *24*(1), 137–147. https://doi.org/10.1080/13607863.2018.1525604

Margolis, S. A., Kelly, D. A., Daiello, L. A., Davis, J., Tremont, G., Pillemer, S., Denby, C., & Ott, B. R. (2021). Anticholinergic/sedative drug burden and subjective cognitive decline in older adults at risk of Alzheimer's disease. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *76*(6), 1037–1043. https://doi.org/10.1093/gerona/glaa222

Marian, V., Blumenfeld, H. K., & Kaushanskaya, M. (2007). The Language Experience and Proficiency Questionnaire (LEAP-Q): Assessing language profiles in bilinguals and multilinguals. *Journal of Speech, Language, and Hearing Research*, *50*(4), 940–967. https://doi.org/10.1044/1092-4388(2007/067)

Masyn, K. E. (2012). Latent class analysis and finite mixture modeling. In T. D. Little (Ed.), *The Oxford Handbook of Quantitative Methods* (2nd ed., pp. 551–611). Oxford University Press.

Mathers, C. D., Stevens, G. A., Boerma, T., White, R. A., & Tobias, M. I. (2015). Causes of international increases in older age life expectancy. *The Lancet*, *385*(9967), 540–548. https://doi.org/10.1016/S0140-6736(14)60569-9

Mazure, C. M., & Swendsen, J. (2016). Sex differences in Alzheimer's disease and other dementias. *The Lancet Neurology*, *15*(5), 451–452. https://doi.org/10.1016/S1474-4422(16)00067-3

McDermott, K. L., McFall, G. P., Andrews, S. J., Anstey, K. J., & Dixon, R. A. (2017). Memory resilience to Alzheimer's genetic risk: Sex effects in predictor profiles. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *72*(6), 937–946. https://doi.org/10.1093/geronb/gbw161

McFall, G. P., McDermott, K. L., & Dixon, R. A. (2019). Modifiable risk factors discriminate memory trajectories in non-demented aging: Precision factors and targets for promoting

healthier brain aging and preventing dementia. *Journal of Alzheimer's Disease*, *70*(s1), S101–S118. https://doi.org/10.3233/JAD-180571

McFall, G. P., Wiebe, S. A., Vergote, D., Westaway, D., Jhamandas, J., Bäckman, L., & Dixon, R. A. (2015). ApoE and pulse pressure interactively influence level and change in the aging of episodic memory: Protective effects among ε2 carriers. *Neuropsychology*, *29*(3), 388–401. https://doi.org/10.1037/neu0000150

McGough, E. L., Cochrane, B. B., Pike, K. C., Logdson, R. G., McCurry, S. M., & Teri, L. (2013). Dimensions of physical frailty and cognitive function in older adults with amnestic mild cognitive impairment. *Annals of Physical and Rehabilitation Medicine*, *56*(5), 329–341. https://doi.org/10.1016/j.rehab.2013.02.005

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Mendonça, N., Kingston, A., Yadegarfar, M., Hanson, H., Duncan, R., Jagger, C., & Robinson, L. (2020). Transitions between frailty states in the very old: The influence of socioeconomic status and multi-morbidity in the Newcastle 85+ cohort study. *Age and Ageing*, *49*(6), 974–981. https://doi.org/10.1093/ageing/afaa054

Menon, C., Westervelt, H. J., Jahn, D. R., Dressel, J. A., & O'Bryant, S. E. (2013). Normative performance on the Brief Smell Identification Test (BSIT) in a multi-ethnic bilingual cohort:

A Project FRONTIER study. *Clinical Neuropsychologist*, *27*(6), 946–961. https://doi.org/10.1080/13854046.2013.796406

Merchant, R. A., Goh, J., Chan, Y. H., Lim, J. Y., & Vellas, B. (2021). Slow gait, subjective cognitive decline and motoric cognitive risk syndrome: Prevalence and associated factors in community dwelling older adults. *Journal of Nutrition, Health and Aging*, *25*(1), 48–56. https://doi.org/10.1007/s12603-020-1525-y

Mitnitski, A. B., Molinger, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *The Scientific World*, *1*, 323–336. https://doi.org/10.1100/tsw.2001.58

Mitnitski, Collerton, J., Martin-Ruiz, C., Jagger, C., von Zglinicki, T., Rockwood, K., & Kirkwood, T. B. L. (2015). Age-related frailty and its association with biological markers of ageing. *BMC Medicine*, *13*(1), 1–9. https://doi.org/10.1186/s12916-015-0400-x

Moldovan, M., Khadka, J., Visvanathan, R., Wesselingh, S., & Inacio, M. C. (2020). Using elastic nets to estimate frailty burden from routinely collected national aged care data. *Journal of the American Medical Informatics Association*, *27*(3), 419–428. https://doi.org/10.1093/jamia/ocz210

Monsell, S. E., Dodge, H. H., Zhou, X. H., Bu, Y., Besser, L. M., Mock, C., Hawes, S. E., Kukull, W. A., Weintraub, S., Ferris, S., Kramer, J., Loewenstein, D., Lu, P., Giordani, B., Goldstein, F., Marson, D., Morris, J., Mungas, D., Salmon, D., & Welsh-Bohmer, K. (2016). Results from the NACC Uniform Data Set neuropsychological battery crosswalk study. *Alzheimer Disease and Associated Disorders*, *30*(2), 134–139. https://doi.org/10.1097/WAD.0000000000000111

Montero-Odasso, M., Bergman, H., Béland, F., Sourial, N., Fletcher, J. D., & Dallaire, L. (2009). Identifying mobility heterogeneity in very frail older adults. Are frail people all the same?

Archives of Gerontology and Geriatrics, *49*(2), 272–277. https://doi.org/10.1016/j.archger.2008.09.010

Morin, A. J. S., & Litalien, D. (2017). *Webnote: Longitudinal tests of profile similarity and latent transition analyses*. Substantive Methodological Synergy Research Laboratory.

Morin, A. J. S., Meyer, J. P., Creusier, J., & Biétry, F. (2016). Multiple-group analysis of similarity in latent profile solutions. *Organizational Research Methods*, *19*(2), 231–254. https://doi.org/10.1177/1094428115621148

Morley, J. E., Vellas, B., Abellan van Kan, G., Anker, S. D., Bauer, J. M., Bernabei, R., Cesari, M., Chumlea, W. C., Doehner, W., Evans, J., Fried, L. P., Guralnik, J. M., Katz, P. R., Malmstrom, T. K., McCarter, R. J., Robledo, L. M. G., Rockwood, K., Haehling, S. V., Vandewoude, M. F., & Walston, J. (2013). Frailty consensus: A call to action. *Journal of American Medical Directors Association*, *14*(6), 392–397. https://doi.org/10.1016/j.jamda.2013.03.022

Mourao, R. J., Mansur, G., Malloy-Diniz, L. F., Castro Costa, E., & Diniz, B. S. (2016). Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: Systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, *31*(8), 905–911. https://doi.org/10.1002/gps.4406

Murphy, C. (2019). Olfactory and other sensory impairments in Alzheimer disease. *Nature Reviews Neurology*, *15*(1), 11–24. https://doi.org/10.1038/s41582-018-0097-5

Muthén, B. O., & Muthén, L. K. (2000). Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcoholism: Clinical and Experimental Research*, *24*(6), 882–891. https://doi.org/10.1111/j.1530-0277.2000.tb02070.x

Muthén, L. K., & Muthén, B. O. (2009). *Mplus short courses topic 1: Exploratory factor analysis, confirmatory factor analysis, and structural equation modeling for continuous outcomes*. Muthén & Muthén. http://www.statmodel.com/course_materials.shtml

Muthén, L. K., & Muthén, B. O. (1998-2017). *Mplus user's guide. Eighth Edition.* Muthén & Muthén.

Na, K. S. (2019). Prediction of future cognitive impairment among the community elderly: A machine-learning based approach. *Scientific Reports*, *9*(1), 1–9. https://doi.org/10.1038/s41598-019-39478-7

Nangle, M. R., Riches, J., Grainger, S. A., Manchery, N., Sachdev, P. S., & Henry, J. D. (2019). Oral health and cognitive function in older adults: A systematic review. *Gerontology*, *65*(6), 659–672. https://doi.org/10.1159/000496730

Nari, F., Jang, B. N., Youn, H. M., Jeong, W., Jang, S. I., & Park, E. C. (2021). Frailty transitions and cognitive function among South Korean older adults. *Scientific Reports*, *11*(1), 1–9. https://doi.org/10.1038/s41598-021-90125-6

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Navarro-Martínez, R., & Cauli, O. (2021). Lymphocytes as a biomarker of frailty syndrome: A scoping review. *Diseases*, *9*(53), 1–17. https://doi.org/10.3390/diseases9030053

Ng, S. C. W., Kwan, Y. H., Yan, S., Tan, C. S., & Low, L. L. (2019). The heterogeneous health state profiles of high-risk healthcare utilizers and their longitudinal hospital readmission and

mortality patterns. *BMC Health Services Research*, *19*(1), 1–8. https://doi.org/10.1186/s12913-019-4769-7

Nguyen, Q. D., Wu, C., Odden, M. C., & Kim, D. H. (2019). Multimorbidity patterns, frailty, and survival in community-dwelling older adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *74*(8), 1265–1270. https://doi.org/10.1093/gerona/gly205

Noble, J. M., Scarmeas, N., & Papapanou, P. N. (2013). Poor oral health as a chronic, potentially modifiable dementia risk factor: Review of the literature. *Current Neurology and Neuroscience Reports*, *13*(384), 1–8. https://doi.org/10.1007/s11910-013-0384-x

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences*, *16*(5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005

Nylund-Gibson, K., Grimm, R., Quirk, M., & Furlong, M. (2014). A latent transition mixture model using the three-step specification. *Structural Equation Modeling*, *21*(3), 439–454. https://doi.org/10.1080/10705511.2014.915375

Nylund-Gibson, K., & Choi, A. C. Y. (2018). Ten frequently asked questions about latent class analysis. *Translational Issues in Psychological Science*, *4*(4), 440–461. https://doi.org/http://dx.doi.org/10.1037/tps0000176

Nyunt, M. S. Z., Soh, C. Y., Gao, Q., Gwee, X., Ling, A. S. L., Lim, W. S., Lee, T. S., Yap, P. L. K., Yap, K. B., & Ng, T. P. (2017). Characterisation of physical frailty and associated physical and functional impairments in mild cognitive impairment. *Frontiers in Medicine*, *4*(230), 1–8. https://doi.org/10.3389/fmed.2017.00230

O'Bryant, S. E., Xiao, G., Barber, R., Huebinger, R., Wilhelmsen, K., Edwards, M., Graff-Radford, N., Doody, R., & Diaz-Arrastia, R. (2011). A blood-based screening tool for Alzheimer's

disease that spans serum and plasma: Findings from TARC and ADNI. *PLoS ONE*, *6*(12), 108. https://doi.org/10.1371/journal.pone.0028092

O'Caoimh, R., Galluzzo, L., Rodriguez-Laso, A., van der Heyden, J., Hylen Ranhoff, A., Carcaillon-Bentata, L., Beltzer, N., Kennelly, S., & Liew, A. (2018). Transitions and trajectories in frailty states over time: A systematic review of the European Joint Action ADVANTAGE. *Annali Dell'Istituto Superiore Di Sanita*, *54*(3), 246–252. https://doi.org/10.4415/ANN_18_03_12

Ofori-Asenso, R., Lee Chin, K., Mazidi, M., Zomer, E., Ilomaki, J., Ademi, Z., Bell, J. S., & Liew, D. (2019). Natural regression of frailty among community-dwelling older adults: A systematic review and meta-analysis. *The Gerontologist*, *60I(4)*, e286-e298. https://doi.org/10.1093/geront/gnz064

Olaya, B., Moneta, M. V., Caballero, F. F., Tyrovolas, S., Bayes, I., Ayuso-Mateos, J. L., & Haro, J. M. (2017). Latent class analysis of multimorbidity patterns and associated outcomes in Spanish older adults: A prospective cohort study. *BMC Geriatrics*, *17*, 1–10. https://doi.org/10.1186/s12877-017-0586-1

Panza, F., Lozupone, M., Solfrizzi, V., Sardone, R., Dibello, V., di Lena, L., D'Urso, F., Stallone, R., Petruzzi, M., Giannelli, G., Quaranta, N., Bellomo, A., Greco, A., Daniele, A., Seripa, D., & Logroscino, G. (2018). Different cognitive frailty models and health-and cognitive-related outcomes in older age: From epidemiology to prevention. *Journal of Alzheimer's Disease*, *62*(3), 993–1012. https://doi.org/10.3233/JAD-170963

Panza, F., Solfrizzi, V., Barulli, M. R., Santamato, A., Seripa, D., Pilotto, A., & Logroscino, G. (2015). Cognitive frailty: A systematic review of epidemiological and neurobiological

evidence of an age-related clinical condition. *Rejuvenation Research*, *18*(5), 389–412. https://doi.org/10.1089/rej.2014.1637

Papp, K. V., Kaplan, R. F., Springate, B., Moscufo, N., Wakefield, D. B., Guttmann, C. R. G., & Wolfson, L. (2014). Processing speed in normal aging: Effects of white matter hyperintensities and hippocampal volume loss. *Aging, Neuropsychology, and Cognition*, *21*(2), 197–213. https://doi.org/10.1080/13825585.2013.795513

Paul, R. H., Cho, K. S., Luckett, P., Strain, J. F., Belden, A. C., Bolzenius, J. D., Navid, J., Garcia-Egan, P. M., Cooley, S. A., Wisch, J. K., Boerwinkle, A. H., Tomov, D., Obosi, A., Mannarino, J. A., & Ances, B. M. (2020). Machine learning analysis reveals novel neuroimaging and clinical signatures of frailty in HIV. *Journal of Acquired Immune Deficiency Syndromes*, *84*(4), 414–421. https://doi.org/10.1097/QAI.0000000000002360

Pedregosa, F., Varoquaux, G., Michel, V., Thirion, B., Grisel, O., Blonderl, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., & Duchesnay, E. (2011). Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research*, *12*, 2825–2830. https://doi.org/10.1289/EHP4713

Peng, L. N., Hsiao, F. Y., Lee, W. J., Huang, S. T., & Chen, L. K. (2020). Comparisons between hypothesis- and data-driven approaches for multimorbidity frailty index: A machine learning approach. *Journal of Medical Internet Research*, *22*(6), 1–11. https://doi.org/10.2196/16213

Pérès, K., Helmer, C., Amieva, H., Orgogozo, J. M., Rouch, I., Dartigues, J. F., & Barberger-Gateau, P. (2008). Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: A prospective population-based study. *Journal of the American Geriatrics Society*, *56*(1), 37–44. https://doi.org/10.1111/j.1532-5415.2007.01499.x

Petersen, R. C., Roberts, R. O., Knopman, D. S., Geda, Y. E., Cha, R. H., Pankratz, V. S., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., & Rocca, W. A. (2010). Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic Study of Aging. *Neurology*, *75*(10), 889–897. https://doi.org/10.1212/WNL.0b013e3181f11d85

Pfeiffer, E. (1975). A Short Portable Mental Status Questionnaire for the assessment of organic brain deficit in elderly patients. *Journal of the American Geriatrics Society*, *23*(10), 433–441. https://doi.org/10.1111/j.1532-5415.1975.tb00927.x

Pikoula, M., Quint, J. K., Nissen, F., Hemingway, H., Smeeth, L., & Denaxas, S. (2019). Identifying clinically important COPD sub-types using data-driven approaches in primary care population based electronic health records. *BMC Medical Informatics and Decision Making*, *19*(86), 1–14. https://doi.org/10.1186/s12911-019-0805-0

Pollack, L. R., Harrison, S. L., Cawthon, P. M., Ensrud, K., Lane, N. E., Barrett-Connor, E., & Dam, T. T. (2017). Patterns and predictors of frailty transitions in older men: The Osteoporotic Fractures in Men Study. *Journal of the American Geriatrics Society*, *65*(11), 2473–2479. https://doi.org/10.1111/jgs.15003

Powell, L. E., & Myers, A. M. (1995). The Activities-specific Balance Confidence (ABC) Scale. *Journal of Gerontology: Medical Sciences*, *50*(1), M28–M34. https://doi.org/10.1093/gerona/50a.1.m28

Public Health Agency of Canada. (2019). *A dementia strategy for Canada*. https://www.canada.ca/content/dam/phac-aspc/images/services/publications/diseases-conditions/dementia-strategy/National Dementia Strategy_ENG.pdf

Rankin, D., Black, M., Flanagan, B., Hughes, C. F., Moore, A., Hoey, L., Wallace, J., Gill, C., Carlin, P., Molloy, A. M., Cunningham, C., & McNulty, H. (2020). Identifying key predictors

of cognitive dysfunction in older people using supervised machine learning techniques: Observational study. *JMIR Medical Informatics*, *8*(9), 1–34. https://doi.org/10.2196/20995

Rawle, M. J., Cooper, R., Kuh, D., & Richards, M. (2018). Associations between polypharmacy and cognitive and physical capability: A British birth cohort study. *Journal of the American Geriatrics Society*, *66*(5), 916–923. https://doi.org/10.1111/jgs.15317

Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: Regional and individual differences. *Neuroimage*, *51*(2), 501–511. https://doi.org/10.1016/j.neuroimage.2010.03.020

Reisberg, B., Shulman, M. B., Torossian, C., Leng, L., & Zhu, W. (2010). Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimer's & Dementia*, *6*(1), 1–27. https://doi.org/10.1016/j.jalz.2009.10.002

Rice, M. E., & Harris, G. T. (2005). Comparing effect sizes in follow-up studies: ROC area, Cohen's d, and r. *Law and Human Behavior*, *29*(5), 615–620. https://doi.org/10.1007/s10979-005-6832-7

Riedel, B. C., Thompson, P. M., & Brinton, R. D. (2016). Age, APOE and sex: Triad of risk of Alzheimer's disease. *Journal of Steroid Biochemistry and Molecular Biology*, *160*, 134–147. https://doi.org/10.1016/j.jsbmb.2016.03.012

Risacher, S. L., WuDunn, D., Pepin, S. M., MaGee, T. R., McDonald, B. C., Flashman, L. A., Wishart, H. A., Pixley, H. S., Rabin, L. A., Paré, N., Englert, J. J., Schwartz, E., Curtain, J. R., West, J. D., O'Neill, D. P., Santulli, R. B., Newman, R. W., & Saykin, A. J. (2013). Visual contrast sensitivity in Alzheimer's disease, mild cognitive impairment, and older adults with cognitive complaints. *Neurobiology of Aging*, *34*(4), 1133–1144. https://doi.org/10.1016/j.neurobiolaging.2012.08.007

Risacher, S. L., WuDunn, D., Tallman, E. F., West, J. D., Gao, S., Farlow, M. R., Brosch, J. R., Apostolova, L. G., & Saykin, A. J. (2020). Visual contrast sensitivity is associated with the presence of cerebral amyloid and tau deposition. *Brain Communications*, *2*(1), 1–14. https://doi.org/10.1093/braincomms/fcaa019

Robertson, D. A., Savva, G. M., & Kenny, R. A. (2013). Frailty and cognitive impairment— A review of the evidence and causal mechanisms. *Ageing Research Reviews*, *12*(4), 840–851. https://doi.org/10.1016/j.arr.2013.06.004

Rockwood, K., Andrew, M. K., Aubertin-Leheudre, M., Belleville, S., Bherer, L., Bowles, S. K., Kehler, D. S., Lim, A., Middleton, L., Phillips, N., & Wallace, L. M. K. (2020). CCCDTD5: Reducing the risk of later-life dementia. Evidence informing the Fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD-5). *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *6*(1), 1–12. https://doi.org/10.1002/trc2.12083

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(7), 738–743. https://doi.org/10.1093/gerona/62.7.738

Rockwood, K., & Howlett, S. E. (2018). Fifteen years of progress in understanding frailty and health in aging. *BMC Medicine*, *16*(220), 1–4. https://doi.org/10.1186/s12916-018-1223-3

Rockwood, K., McMillan, M., Mitnitski, A., & Howlett, S. E. (2015). A frailty index based on common laboratory tests in comparison with a clinical frailty index for older adults in long-term care facilities. *Journal of the American Medical Directors Association*, *16*(1), 842–847. https://doi.org/10.1016/j.jamda.2015.03.027

Rockwood, K., Nassar, B., & Mitnitski, A. (2008). Apolipoprotein E-polymorphism, frailty and mortality in older adults. *Journal of Cellular and Molecular Medicine*, *12*(6B), 2754–2761. https://doi.org/10.1111/j.1582-4934.2008.00270.x

Rodriguez-Mañas, L., Carvalho, I. A. de, Bhasin, S., Bischoff-Ferrari, H. A., Cesari, M., Evans, W., Hare, J. M., Pahor, M., Parini, A., Rolland, Y., Fielding, R. A., Walston, J., Vellas, B., & ICFSR Task Force. (2020). ICFSR task force perspective on biomarkers for sarcopenia and frailty. *The Journal of Frailty & Aging*, *9*(1), 4–8. https://doi.org/10.14283/jfa.2019.32

Roehr, S., Riedel-Heller, S. G., Kaduszkiewicz, H., Wagner, M., Fuchs, A., van der Leeden, C., Wiese, B., Werle, J., Bickel, H., König, H. H., Wolfsgruber, S., Pentzek, M., Weeg, D., Mamone, S., Weyerer, S., Brettschneider, C., Maier, W., Scherer, M., Jessen, F., & Luck, T. (2019). Is function in instrumental activities of daily living a useful feature in predicting Alzheimer's disease dementia in subjective cognitive decline? *International Journal of Geriatric Psychiatry*, *34*(1), 193–203. https://doi.org/10.1002/gps.5010

Rogers, N. T., Marshall, A., Roberts, C. H., Demakakos, P., Steptoe, A., & Scholes, S. (2017). Physical activity and trajectories of frailty among older adults: Evidence from the English Longitudinal Study of Ageing. *PLoS ONE*, *12*(2), 1–12. https://doi.org/10.1371/journal.pone.0170878

Rohrmann, S. (2020). Epidemiology of frailty in older people. *Advances in Experimental Medicine and Biology*, *1216*, 21–27. https://doi.org/10.1007/978-3-030-33330-0_3

Rolfson, D. B., Wilcock, G., Mitnitski, A., King, E., De Jager, C. A., Rockwood, K., Fallah, N., & Searle, S. D. (2013). An assessment of neurocognitive speed in relation to frailty. *Age and Ageing*, *42*(2), 191–196. https://doi.org/10.1093/ageing/afs185

Romero-Ortuno, R., & O'Shea, D. (2013). Fitness and frailty: Opposite ends of a challenging continuum! Will the end of age discrimination make frailty assessments an imperative? *Age and Ageing*, *42*(3), 279–280. https://doi.org/10.1093/ageing/afs189

Ruan, Q., Xiao, F., Gong, K., Zhang, W., Zhang, M., Ruan, J., Zhang, X., Chen, Q., & Yu, Z. (2020). Prevalence of cognitive frailty phenotypes and associated factors in a community-dwelling elderly population. *Journal of Nutrition, Health and Aging*, *24*(2), 172–180. https://doi.org/10.1007/s12603-019-1286-7

Ryoo, J. H., Wang, C., Swearer, S. M., Hull, M., & Shi, D. (2018). Longitudinal model building using latent transition analysis: An example using school bullying data. *Frontiers in Psychology*, *9*(675), 1–13. https://doi.org/10.3389/fpsyg.2018.00675

Sachdev, P. S., Anstey, K. J., Parslow, R. A., Wen, W., Maller, J., Kumar, R., Christensen, H., & Jorm, A. F. (2006). Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. *Dementia and Geriatric Cognitive Disorders*, *21*(5-6), 300–308. https://doi.org/10.1159/000091438

Sadiq, F., Kronzer, V. L., Wildes, T. S., McKinnon, S. L., Sharma, A., Helsten, D. L., Scheier, L. M., Avidan, M. S., & Abdallah, A. B. (2018). Frailty phenotypes and relations with surgical outcomes. *Anesthesia & Analgesia*, *127*(4), 1017–1027. https://doi.org/10.1213/ANE.0000000000003695

Sapkota, S., Huan, T., Tran, T., Zheng, J., Camicioli, R., Li, L., & Dixon, R. A. (2018). Alzheimer's biomarkers from multiple modalities selectively discriminate clinical status: Relative importance of salivary metabolomics panels, genetic, lifestyle, cognitive, functional health and demographic risk markers. *Frontiers in Aging Neuroscience*, *10*(296), 1–13. https://doi.org/10.3389/fnagi.2018.00296

Sarksian, C. A., Gruenewald, T. L., Boscardin, J., & Seeman, T. E. (2008). Preliminary evidence for subdimensions of geriatric frailty: The MacArthur Study of Successful Aging. *Journal of the American Geriatrics Society*, *56*(12), 2292–2297. https://doi.org/doi:10.1111/j.1532-5415.2008.02041.x

Sathyan, S., Ayers, E., Gao, T., Milman, S., Barzilai, N., Rockwood, K., & Verghese, J. (2019). Frailty and risk of incident motoric cognitive risk syndrome. *Journal of Alzheimer's Disease*, *71*(Suppl 1), S85–S93. https://doi.org/10.3233/JAD-190517

Schiepers, O. J. G., Harris, S. E., Gow, A. J., Pattie, A., Brett, C. E., Starr, J. M., & Deary, I. J. (2012). APOE E4 status predicts age-related cognitive decline in the ninth decade: Longitudinal follow-up of the Lothian Birth Cohort 1921. *Molecular Psychiatry*, *17*, 315–324. https://doi.org/10.1038/mp.2010.137

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics*, *8*(24), 1–10. https://doi.org/10.1186/1471-2318-8-24

Searle, S. D., & Rockwood, K. (2015). Frailty and the risk of cognitive impairment. *Alzheimer's Research & Therapy*, *7*(54), 1–6. https://doi.org/10.1186/s13195-015-0140-3

Seaton, E. K., Yip, T., Morgan-Lopez, A., & Sellers, R. M. (2012). Racial discrimination and racial socialization as predictors of African American adolescents' racial identity development using latent transition analysis. *Developmental Psychology*, *48*(2), 448–458. https://doi.org/10.1037/a0025328

Segal, J. B., Chang, H. Y., Du, Y., Walson, J., Carlson, C., & Varadhan, R. (2017). Development of a claims-based frailty indicator anchored to a well-established frailty phenotype. *Medical Care*, *55*(7), 716–722. https://doi.org/10.1097/MLR.0000000000000729

Segaux, L., Oubaya, N., Broussier, A., Baude, M., Canouï-Poitrine, F., Naga, H., Laurent, M., Leissing-Desprez, C., Audureau, E., Ferrat, E., Chailloleau, C., Fromentin, I., David, J. P., & Bastuji-Garin, S. (2019). Identification of five frailty profiles in community-dwelling individuals aged 50–75: A latent class analysis of the SUCCEED survey data. *Maturitas*, *127*(3), 1–11. https://doi.org/10.1016/j.maturitas.2019.05.007

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., Kwak, Y., & Lipps, D. B. (2010). Motor control and aging: Links to age-related brain structural, functional, and biochemical effects. *Neuroscience and Biobehavioral Reviews*, *34*(5), 721–733. https://doi.org/10.1016/j.neubiorev.2009.10.005

Smith, L., Shin, J. il, Jacob, L., López-Sánchez, G. F., Oh, H., Barnett, Y., Pardhan, S., Butler, L., Soysal, P., Veronese, N., & Koyanagi, A. (2021). The association between objective vision impairment and mild cognitive impairment among older adults in low- and middle-income countries. *Aging Clinical and Experimental Research*, *33*, 2695–2702. https://doi.org/10.1007/s40520-021-01814-1

Solfrizzi, V., Scafato, E., Frisardi, V., Seripa, D., Logroscino, G., Maggi, S., Imbimbo, B. P., Galluzzo, L., Baldereschi, M., Gandin, C., di Carlo, A., Inzitari, D., Crepaldi, G., Pilotto, A., & Panza, F. (2013). Frailty syndrome and the risk of vascular dementia: The Italian Longitudinal Study on Aging. *Alzheimer's and Dementia*, *9*(2), 113–122. https://doi.org/10.1016/j.jalz.2011.09.223

Song, X., Mitnitski, A., Cox, J., & Rockwood, K. (2004a). Comparison of machine learning techniques with classical statistical models in predicting health outcomes. *Studies in Health Technology and Informatics*, *107*, 736–740. https://doi.org/10.3233/978-1-60750-949-3-736

Song, X., Mitnitski, A., MacKnight, C., & Rockwood, K. (2004b). Assessment of individual risk of death using self-report data: An artificial neural network compared with a frailty index. *Journal of the American Geriatrics Society*, *52*(7), 1180–1184. https://doi.org/10.1111/j.1532-5415.2004.52319.x

Song, X., Mitnitski, A., & Rockwood, K. (2014). Age-related deficit accumulation and the risk of late-life dementia. *Alzheimer's Research & Therapy*, *6*(54), 1–13. https://doi.org/http://alzres.com/content/6/5/54

Soria-Comes, T., Palomar-Abril, V., Ureste, M. M., Sánchez, J. G., Buades, J. E. M., Llavador, M. J. F., Gabaldón, A. L., Jurado, M. G., & Maiques, I. C. M. (2020). T-lymphocytes in older patients diagnosed with non-small cell lung cancer (NSCLC). *Translational Cancer Research*, *9*(11), 6857-6866. http://dx.doi.org/10.21037/tcr-20-1997

Sourial, N., Bergman, H., Karunananthan, S., Wolfson, C., Guralnik, J., Payette, H., Gutierrez-Robledo, L., Deeg, D. J. H., Fletcher, J. D., Puts, M. T. E., Zhu, B., & Béland, F. (2012). Contribution of frailty markers in explaining differences among individuals in five samples of older persons. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *67*(11), 1197–1204. https://doi.org/10.1093/gerona/gls084

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, 7(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Sternäng, O., Reynolds, C. A., Finkel, D., Ernsth-Bravell, M., Pedersen, N. L., & Dahl Aslan, A. K. (2016). Grip strength and cognitive abilities: Associations in old age. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *71*(5), 841–848. https://doi.org/10.1093/geronb/gbv017

Stewart, R. (2012). Subjective cognitive impairment. *Current Opinion in Psychiatry*, *25*(6), 445–450. https://doi.org/10.1097/YCO.0b013e3283586fd8

Subudhi, S., Verma, A., Patel, A. B., Hardin, C. C., Khandekar, M. J., Lee, H., McEvoy, D., Stylianopoulos, T., Munn, L. L., Dutta, S., & Jain, R. K. (2021). Comparing machine learning algorithms for predicting ICU admission and mortality in COVID-19. n*pj Digital Medicine*, *4*(87), 1–7. https://doi.org/10.1038/s41746-021-00456-x

Sugimoto, K., Rakugi, H., Kojima, T., Ishii, S., Akishita, M., Tamura, Y., Araki, A., Kozaki, K., Senda, K., Fukuoka, H., Satake, S., & Arai, H. (2020). Chapter 4 Frailty and specific diseases. *Geriatrics and Gerontology International*, *20*(S1), 25–37. https://doi.org/10.1111/ggi.13833

Sugimoto, T., Sakurai, T., Ono, R., Kimura, A., Saji, N., Niida, S., Toba, K., Chen, L. K., & Arai, H. (2018). Epidemiological and clinical significance of cognitive frailty: A mini review. *Ageing Research Reviews*, *44*, 1–7. https://doi.org/10.1016/j.arr.2018.03.002

Tarekegn, A., Ricceri, F., Costa, G., Ferracin, E., & Giacobini, M. (2020). Predictive modeling for frailty conditions in elderly people: Machine learning approaches. *JMIR Medical Informatics*, *8*(6), 1–16. https://doi.org/10.2196/16678

Tay, L., Lim, W. S., Chan, M., Ye, R. J., & Chong, M. S. (2016). The independent role of inflammation in physical frailty among older adults with mild cognitive impairment and mild-to-moderate Alzheimer's disease. *Journal of Nutrition, Health and Aging*, *20*(3), 288–299. https://doi.org/10.1007/s12603-015-0617-6

Theou, O., Squires, E., Mallery, K., Lee, J. S., Fay, S., Goldstein, J., Armstrong, J. J., & Rockwood, K. (2018). What do we know about frailty in the acute care setting? A scoping review. *BMC Geriatrics*, *18*(1). https://doi.org/10.1186/s12877-018-0823-2

Theou, O., Tan, E. C. K., Bell, J. S., Emery, T., Robson, L., Morley, J. E., Rockwood, K., & Visvanathan, R. (2016). Frailty levels in residential aged care facilities measured using the frailty index and FRAIL-NH scale. *Journal of the American Geriatrics Society*, *64*(11), e207–e212. https://doi.org/10.1111/jgs.14490

Thibeau, S., McDermott, K., McFall, G. P., Rockwood, K., & Dixon, R. A. (2019). Frailty effects on non-demented cognitive trajectories are moderated by sex and Alzheimer's genetic risk. *Alzheimer's Research & Therapy*, *11*(55), 1–15. https://doi.org/https://doi.org/10.1186/s13195-019-0509-9

Thompson, M. Q., Theou, O., Adams, R. J., Tucker, G. R., & Visvanathan, R. (2018). Frailty state transitions and associated factors in South Australian older adults. *Geriatrics and Gerontology International*, *18*(11), 1549–1555. https://doi.org/10.1111/ggi.13522

Tierney, M. C., Curtis, A. F., Chertkow, H., & Rylett, R. J. (2017). Integrating sex and gender into neurodegeneration research: A six-component strategy. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *3*(4), 660–667. https://doi.org/10.1016/j.trci.2017.10.006

Tomás, J. M., Sentandreu-Mañó, T., & Fernández, I. (2020). Frailty status typologies in Spanish older population: Associations with successful aging. *International Journal of Environmental Research and Public Health*, *17*(18), 1–12. https://doi.org/10.3390/ijerph17186772

Trevisan, C., Rizzuto, D., Maggi, S., Sergi, G., Welmer, A. K., & Vetrano, D. L. (2019). Cross-sectional and longitudinal associations between peak expiratory flow and frailty in older adults. *Journal of Clinical Medicine*, *8*(11), 1–12. https://doi.org/10.3390/jcm8111901

Trevisan, C., Veronese, N., Maggi, S., Baggio, G., Toffanello, E. D., Zambon, S., Sartori, L., Musacchio, E., Perissinotto, E., Crepaldi, G., Manzato, E., & Sergi, G. (2017). Factors influencing transitions between frailty states in elderly adults: The Progetto Veneto Anziani Longitudinal Study. *Journal of the American Geriatrics Society*, *65*(1), 179–184. https://doi.org/10.1111/jgs.14515

Vaz Fragoso, C. A., Enright, P. L., McAvay, G., Van Ness, P. H., & Gill, T. M. (2012). Frailty and respiratory impairment in older persons. *American Journal of Medicine*, *125*(1), 79–86. https://doi.org/10.1016/j.amjmed.2011.06.024

Velayudhan, L. (2015). Smell identification function and Alzheimer's disease: A selective review. *Current Opinion in Psychiatry*, *28*(2), 173–179. https://doi.org/10.1097/YCO.0000000000000146

Ventry, I. M., & Weinstein, B. E. (1982). The Hearing Handicap Inventory for the Elderly: A new tool. *Ear and Hearing*, *3*(3), 128–134. https://doi.org/10.1097/00003446-198205000-00006

Verghese, J., Ayers, E., Sathyan, S., Lipton, R. B., Milman, S., Barzilai, N., & Wang, C. (2021). Trajectories of frailty in aging: Prospective cohort study. *PLoS ONE*, *16*(7), 1–14. https://doi.org/10.1371/journal.pone.0253976

Vermeiren, S., Vella-Azzopardi, R., Beckwée, D., Habbig, A. K., Scafoglieri, A., Jansen, B., Bautmans, I., Bautmans, I., Verté, D., Beyer, I., Petrovic, M., De Donder, L., Kardol, T., Rossi, G., Clarys, P., Scafoglieri, A., Cattrysse, E., de Hert, P., & Jansen, B. (2016). Frailty and the prediction of negative health outcomes: A meta-analysis. *Journal of the American*

Medical Directors Association, *17*(12), 1163.e1-1163.e17. https://doi.org/10.1016/j.jamda.2016.09.010

Vermunt, J. K. (2010). Latent class modeling with covariates: Two improved three-step approaches. *Political Analysis*, *18*(4), 450–469. https://doi.org/10.1093/pan/mpq025

Wallace, L., Theou, O., Godin, J., Andrew, M. K., Bennett, D. A., & Rockwood, K. (2019). Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: A cross-sectional analysis of data from the Rush Memory and Aging Project. *The Lancet Neurology*, *18*(2), 177–184. https://doi.org/10.1016/S1474-4422(18)30371-5

Wallace, L., Theou, O., Rockwood, K., & Andrew, M. K. (2018). Relationship between frailty and Alzheimer's disease biomarkers: A scoping review. *Alzheimer's & Dementia: Diagnosis, Assessment and Disease Monitoring*, *10*, 394–401. https://doi.org/10.1016/j.dadm.2018.05.002

Walston, J., Buta, B., & Xue, Q. L. (2018). Frailty screening and interventions: Considerations for clinical practice. *Clinics in Geriatric Medicine*, *34*(1), 25–38. https://doi.org/10.1016/j.cger.2017.09.004

Walston, J., Hadley, E. C., Ferrucci, L., Guralnik, J. M., Newman, A. B., Studenski, S. A., Ershler, W. B., Harris, T., & Fried, L. P. (2006). Research agenda for frailty in older adults: Toward a better understanding of physiology and etiology: Summary from the American Geriatrics Society/National Institute on Aging research conference on frailty in older adults. *Journal of the American Geriatrics Society*, *54*(6), 991–1001. https://doi.org/10.1111/j.1532-5415.2006.00745.x

Wang, J., Maxwell, C. A., & Yu, F. (2019). Biological processes and biomarkers related to frailty in older adults: A state-of-the-science literature review. *Biological Research for Nursing*, *21*(1), 80–106. https://doi.org/10.1177/1099800418798047

Ward, D. D., Wallace, L. M. K., & Rockwood, K. (2021a). Cumulative health deficits, APOE genotype, and risk for later-life mild cognitive impairment and dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, *92*(2), 136–142. https://doi.org/10.1136/jnnp-2020-324081

Ward, D. D., Wallace, L. M. K., & Rockwood, K. (2021b). Frailty and risk of dementia in mild cognitive impairment subtypes. *Annals of Neurology*, *89*(6), 1221–1225. https://doi.org/10.1002/ana.26064

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): Development and evaluation. *Journal of Clinical Epidemiology*, *46*(2), 153–162. https://doi.org/10.1016/0895-4356(93)90053-4

Weintraub, S., Besser, L., Dodge, H. H., Teylan, M., Ferris, S., Goldstein, F. C., Giordani, B., Kramer, J., Loewenstein, D., Marson, D., Mungas, D., Salmon, D., Welsh-Bohmer, K., Zhou, X. H., Shirk, S. D., Atri, A., Kukull, W. A., Phelps, C., & Morris, J. C. (2018). Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). *Alzheimer Disease and Associated Disorders*, *32*(1), 10–17. https://doi.org/10.1097/WAD.0000000000000223

Welstead, M., Jenkins, N. D., Russ, T. C., Luciano, M., & Muniz-Terrera, G. (2020). A systematic review of frailty trajectories: Their shape and influencing factors. *The Gerontologist*, *61*(8), e463-e475. https://doi.org/10.1093/geront/gnaa061

Wen, Y. C., Chen, L. K., & Hsiao, F. Y. (2017). Predicting mortality and hospitalization of older adults by the multimorbidity frailty index. *PLoS ONE*, *12*(11), 1–10. https://doi.org/10.1371/journal.pone.0187825

Wennberg, A. M. v., Wu, M. N., Rosenberg, P. B., & Spira, A. P. (2017). Sleep disturbance, cognitive decline, and dementia: A review. *Seminars in Neurology*, *37*(4), 395–406. https://doi.org/10.1055/s-0037-1604351

Whitson, H. E., Johnson, K. S., Sloane, R., Cigolle, C. T., Pieper, C. F., Landerman, L., & Hastings, S. N. (2016). Identifying patterns of multimorbidity in older Americans: Application of latent class analysis. *Journal of the American Geriatrics Society*, *64*(8), 1668–1673. https://doi.org/10.1111/jgs.14201

WHOQOL Group. (1998). World Health Organization Quality of Life Assessment (WHOQOL): Development and general psychometric properties. *Social Science and Medicine*, *46*(12), 1569–1585. https://doi.org/10.1016/S0277-9536(98)00009-4

Wilmoth, J. R. (2000). Demography of longevity: Past, present, and future trends. *Experimental Gerontology*, *35*(9-10), 1111–1129. https://doi.org/10.1016/S0531-5565(00)00194-7

Wolf, D. S., Gearing, M., Snowdon, D. A., Mori, H., Markesbery, W. R., & Mirra, S. S. (1999). Progression of regional neuropathology in Alzheimer disease and normal elderly: Findings from the Nun study. *Alzheimer Disease and Associated Disorders*, *13*(4), 226–231. https://doi.org/10.1097/00002093-199910000-00009

Wong, T. T. (2015). Performance evaluation of classification algorithms by k-fold and leave-one-out cross validation. *Pattern Recognition*, *48*(9), 2839–2846. https://doi.org/10.1016/j.patcog.2015.03.009

Wong, Y. J., Nguyen, C. P., Wang, S.-Y., Chen, W., Steinfeldt, J. A., & Kim, B. S. K. (2012). A latent profile analysis of Asian American men's and women's adherence to cultural values. *Cultural Diversity and Ethnic Minority Psychology*, *18*(3), 258–267. https://doi.org/10.1037/a0028423

Woods, R. T., Nelis, S. M., Martyr, A., Roberts, J., Whitaker, C. J., Markova, I., Roth, I., Morris, R., & Clare, L. (2014). What contributes to a good quality of life in early dementia? Awareness and the QoL-AD: A cross-sectional study. *Health and Quality of Life Outcomes*, *12*(94), 1–11. https://doi.org/10.1186/1477-7525-12-94

World Bank (2020, December 15). *Population ages 65 and above (% of total population)*. https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS?end=2019&start=1960

Wu, Y. H., Liu, L. K., Chen, W. T., Lee, W. J., Peng, L. N., Wang, P. N., & Chen, L. K. (2015). Cognitive function in individuals with physical frailty but without dementia or cognitive complaints: Results from the I-Lan Longitudinal Aging Study. *Journal of American Medical Directors Association*, *16*(10), 899.e9-899.e16. https://doi.org/10.1016/j.jamda.2015.07.013

Yaffe, K., Fiocco, A. J., Lindquist, K., Vittinghoff, E., Simonsick, E. M., Newman, A. B., Satterfield, S., Rosano, C., Rubin, S. M., Ayonayon, H. N., & Harris, T. B. (2009). Predictors of maintaining cognitive function in older adults: The Health ABC Study. *Neurology*, *72*(23), 2029–2035. https://doi.org/10.1212/WNL.0b013e3181a92c36

Yesavage, J. A., & Sheikh, J. I. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist*, *5*(1-2), 165–173. https://doi.org/10.1300

Yuan, Y., Lapane, K. L., Tjia, J., Baek, J., Liu, S. H., & Ulbricht, C. M. (2021). Physical frailty and cognitive impairment in older nursing home residents: A latent class analysis. *BMC Geriatrics*, *21*(1), 1–12. https://doi.org/10.1186/s12877-021-02433-1

Zacarías-Pons, L., Vilalta-Franch, J., Turró-Garriga, O., Saez, M., & Garre-Olmo, J. (2021). Multimorbidity patterns and their related characteristics in European older adults: A longitudinal perspective. *Archives of Gerontology and Geriatrics*, *95*(104428), 1–7. https://doi.org/10.1016/j.archger.2021.104428

Zahodne, L. B., Schupf, N., Brickman, A. M., Mayeux, R., Wall, M. M., Stern, Y., & Manly, J. J. (2016). Dementia risk and protective factors differ in the context of memory trajectory groups. *Journal of Alzheimer's Disease*, *52*(3), 1013–1020. https://doi.org/10.3233/JAD-151114

Zammit, A. R., Robitaille, A., Piccinin, A. M., Muniz-Terrera, G., & Hofer, S. M. (2019). Associations between aging-related changes in grip strength and cognitive function in older adults: A systematic review. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *74*(4), 519–527. https://doi.org/10.1093/gerona/gly046

Zhang, Y., Xu, X. J., Lian, T. Y., Huang, L. F., Zeng, J. M., Liang, D. M., Yin, M. J., Huang, J. X., Xiu, L. C., Yu, Z. W., Li, Y. L., Mao, C., & Ni, J. D. (2020). Development of frailty subtypes and their associated risk factors among the community-dwelling elderly population. *Aging*, *12*(2), 1128–1140. https://doi.org/10.18632/aging.102671

Appendix A

This appendix contains the final supplementary material for Chapter 2: *Portals to frailty? Data-Driven Analyses Detect Early Frailty Profiles* (Bohn et al., 2021).

Supplementary Methods

Measures

Simple reaction time. Participants were shown a warning stimulus, followed by a signal stimulus, in the middle of a computer screen. Participants were asked to press a response key as quickly as possible upon detecting the signal stimulus. Participants completed 10 practice trials, followed by 50 test trials. Ten randomly arranged trials were presented at each of the 5 intervals separating the warning and signal stimulus (i.e., 500, 625, 750, 875, and 1,000 ms).

Choice reaction time. Participants were presented with a 2 x 2 grid on the computer screen and instructed that one of the plus signs would be replaced by a square (following a 1000 ms delay). Their task was to indicate the location of the square as quickly as possible by pressing the corresponding key on the response console.

Lexical decision. Participants were shown a string of five to seven letters on the computer screen and informed that their task was to identify, as quickly as possible, whether the letters formed an English word (e.g., *island vs. nabion*). Participants completed 3 practice trials, followed by 60 test trials (30 words and 30 nonwords).

Sentence verification. Participants were presented with a sentence on a computer screen and subsequently asked to determine the plausibility of the sentence as quickly as possible (e.g., *The tree fell to the ground with a loud crash* vs. *The pig gave birth to a litter of kittens this morning*). Participants were administered 4 practice trials, followed by 50 test trials.

Correction procedures. We trimmed extreme outliers from raw latency scores using validated correction procedures (Dixon et al., 2007; McFall et al., 2015). Specifically, we applied the following lower and upper limits for each task: (a) simple reaction time: 150 ms lower limit, 2500 ms upper limit, (b) choice reaction time: 150 ms lower limit, 4000 ms upper limit, (c) lexical decision: 400 ms lower limit, 10,000 ms upper limit, and (d) sentence verification: 1000 ms lower limit, 20,000 ms upper limit. We used task-specific lower and upper limits in order to account for variability across tasks in cognitive complexity. We removed trials that fell three standard deviations above or below the sample mean.

Foundational analyses

Confirmatory factor analysis. We determined statistical model fit using the following standard indices: (a) $\chi 2$ for which a good fit would produce a non-significant result (i.e., $p > .05$; indicates that the data do not significantly differ from model-based estimates), (b) the comparative fit index (CFI) for which fit is judged by a value of $\geq .95$ as good and $\geq .90$ as adequate, (c) root mean square error of approximation (RMSEA) for which fit is judged by a value of $\leq .05$ as good and $\leq .08$ as adequate, and (d) standardized root mean square residual (SRMR) for which fit is judged by a value of $\leq .08$ as good (Little, 2013).

Longitudinal measurement invariance. We tested longitudinal measurement invariance of the speed latent variable by evaluating (a) configural invariance (the same factor loading patterns over time); (b) metric invariance (the same factor loadings over time); and (c) scalar invariance (the same intercepts over time). We tested invariance assumptions by comparing models with unconstrained and constrained parameters using change in CFI, for which changes of $\leq .01$ suggest the assumption is reasonable (Little, 2013).

Unconditional latent growth modeling. In order to establish the functional form of speed, we estimated factor scores and employed these in an unconditional latent growth model. Age was centered at 75 years for the growth model because (a) this is the approximate mean of the 40-year span of data, (b) this as a common inflection point for such age spans in cognitive aging research (Dixon et al., 2012), and (c) this is standard practice in VLS research (McFall et al., 2015). We established the best model by testing the following models in sequence (a) a fixed intercept model, which assumes no intra- or inter-individual variability; (b) a random intercept model, which allows for interindividual differences in overall level but assumes no intraindividual change; (c) a random intercept fixed slope model, which allows for interindividual differences in level but assumes that each person changes at a comparable rate; and (d) a random intercept random slope model, which allows for interindividual differences in both level and change (Singer & Willett, 2003).

Table S1. *Complete List of 50 Items Submitted to an Exploratory Factor Analysis*

	Frailty Item	Coding
SR	Stroke	0 = no; 0.33 = yes, not serious; 0.67 = yes, moderately serious; 1 = yes, very serious
	Thyroid condition	
	Arthritis (rheumatoid and/or osteo-)	
	Osteoporosis	
	Cancer	
	Asthma	
	Migraines	
	Stomach ulcer	
	Kidney or bladder trouble	
	Gastrointestinal problems (colitis/diverticulitis, gall bladder trouble, and/or liver trouble)	
	Bronchitis or emphysema	
	Diabetes	
	High blood pressure	
	Sex-related health problems (i.e., gynecological problems or prostate problems)	
	Anaemia	
	Drug and/or alcohol dependence	
	Spinal condition and/or back trouble	
	Hardening of arteries (i.e., atherosclerosis)	
	Heart trouble	
	Other conditions (up to three)	
SR	Number of medications	0 = 0-3; 0.5 = 4-7; 1 = 8+
SR	Subjective health relative to a perfect state of health	0 = very good; 0.25 = good; 0.50 = fair; 0.75 = poor; 1 = very poor
	Eyesight relative to age group	
	Hearing relative to age group	
SR	Health has affected ability to do chores	0 = no change, improved, N/A; 0.25 = slightly reduced; 0.50 = moderately
	Health has affected ability to get around town	

	Health has affected ability to do mental recreational activities Health has affected ability to do physical recreational activities Health has affected ability to do hobbies Health has affected ability to socialize Health has affected ability to travel	reduced; 0.75 = drastically reduced; 1 = gave up doing activity
SR	Stay at home but in chair most of the time	0 = no; 1 = yes
SR	Number of times sick in bed all day in the past year	0 = 0-3; 1 = 4+
SR	Number of times confined to hospital in the past year	0 = 0; 0.5 = 1-2; 3+ = 1
SR	Feeling short of breath	0 = no; 1 = yes
SR	Use of a walker, cane, or wheelchair	0 = no; 1 = yes
M	Resting heart rate (bpm)	0 = 60-99; 1 = < 60 or 100+
M	Pulse pressure (mmHg)	0 = 32.13-63.90; 0.5 = 64-75.9; 1 = 76+
M	Peak expiratory flow (L/min)	Men: 0 = >340; 1 = ≤340 Women: 0 = >310; 1 = ≤ 310
M	Body mass index (kg/m^2)	0 = 18.5-25; 0.5 = 25 to < 30; 1 = < 18.5 or ≥ 30
M	Grip strength (kg)	Men: for BMI ≤ 24, GS ≤ 29; for BMI 24.1-28, GS ≤ 30; for BMI > 28, GS ≤ 32 Women: for BMI ≤ 23, GS ≤ 17; for BMI 23.1-26, GS ≤ 17.3; for BMI 26.1-29, GS ≤ 18; for BMI > 29, GS ≤ 21
M	Timed walk	0 = ≤10s; 1 = >10s
M	Timed turn	0 = < 90th percentile 1 = within 90th percentile

M	Finger dexterity	0 = < 90th percentile 1 = within 90th percentile
SR	CES-D "during the past week, my sleep was restless"	0 = rarely or none of the time; 0.33 = some or a little of the time; 0.67 = occasionally or a moderate amount of the time; 1 = most or all of the time
SR	CES-D "during the past week, I felt depressed"	
SR	CES-D "during the past week, I felt lonely"	
SR	CES-D "during the past week, I could not get going"	
SR	Bradburn negative affect (restless, lonely, bored, depressed, upset due to criticism)	0 = no to all; 0.2 = yes to one; 0.4 = yes to two; 0.6 = yes to three; 0.8 = yes to four; 1 = yes to all
SR	Physical activity at least 2-3 times per week	0 = yes; 1 = no

Note. SR, self-reported; M, measured; CES-D, Center for Epidemiological Studies Depression Scale.

Table S2. *Fit Indices for Confirmatory Factor Analysis and Measurement Invariance Testing for Neurocognitive Speed*

Model	AIC	BIC	χ^2	*df*	*p*	RMSEA	CFI	SRMR	ΔCFI
Configural invariance	19013.62	19268.72	217.23	33	<.001	.09 (.08 - .11)	.96	.08	--
Metric invariance	19010.57	19238.82	226.187	39	<.001	.09 (.08 - .10)	.96	.09	<.01
Scalar invariance [a]	19022.97	19224.36	250.58	45	<.001	.08 (.07 - .09)	.96	.09	<.01

Note. AIC, Akaike information criterion; BIC, Bayesian information criterion; χ2, chi-square test of model fit; *df*, degrees of freedom for model fit; RMSEA, root mean square error of approximation; RMSEA is shown with 90% confidence intervals; CFI, comparative fit index; SRMR, standardized root mean square residual; ΔCFI = change in CFI.

[a] Best fitting model.

Table S3. *Fit Indices for the Unconditional Growth Model for Neurocognitive Speed and the Frailty Index*

Model	(-)2*LL*	npar free	AIC	*BIC*	*D*	Δ*df*
Neurocognitive Speed						
Fixed intercept	5000.61	4	5008.61	5026.51	--	--
Random intercept	3961.54	5	3971.54	3993.92	1039.07*	1
Random intercept, fixed slope	3254.56	6	3266.56	3293.41	706.98*	1
Random intercept, random slope [a]	2996.75	8	3012.75	3048.55	257.81*	2
Frailty Index						
Fixed intercept	-3274.39	4	-3200.11	-3182.30	--	--
Random intercept	-3887.54	5	-3811.64	-3789.38	-607.07*	1
Random intercept, fixed slope	-3836.62	6	-3746.72	-3720.01	69.37	1
Random intercept, random slope [a]	-4109.26	8	-4015.40	-3979.78	-259.78*	2

Note. -2*LL*, -2 log-likelihood; npar, number of parameters; AIC, Akaike information criterion; BIC, Bayesian information criterion; *D*, difference statistic. [a] Best fitting model.

* $p < .001$

Table S4. *Model Estimated Class-Specific Means and Standardized Mean Differences for Each Indicator*

	Not-clinically-frail	Mobility-type	Respiratory-type	Standardized mean differences		
Indicator	542 (84%)	59 (9%)	48 (7%)	MTF - NCF	RTF - NCF	MTF - RTF
Physical activity	0.16 (0.16)	0.29 (0.20)	0.27 (0.22)	0.75	0.67	0.11
Cardiac symptoms	0.07 (0.10)	0.17 (0.17)	0.10 (0.11)	0.86	0.24	0.78
Respiratory symptoms	0.03 (0.05)	0.03 (0.08)	0.46 (0.13)	0.14	**6.96**	**-4.72**
Comorbidity	0.12 (0.14)	0.12 (0.14)	0.19 (0.21)	0.01	0.56	-0.52
Emotional well-being	0.19 (0.18)	0.16 (0.14)	0.24 (0.18)	-0.14	0.28	-0.55
Instrumental health	0.06 (0.10)	0.20 (0.17)	0.12 (0.13)	1.31	0.60	0.80
Mobility	0.05 (0.10)	0.58 (0.14)	0.12 (0.17)	**5.09**	0.61	**3.90**

Note. Results presented as mean (standard deviation). Indicators are coded such that higher scores denote greater impairment. Bolded values represent indicators with a high degree of class separation. NCF, not-clinically-frail; MTF, mobility-type frailty; RTF, respiratory-type frailty.

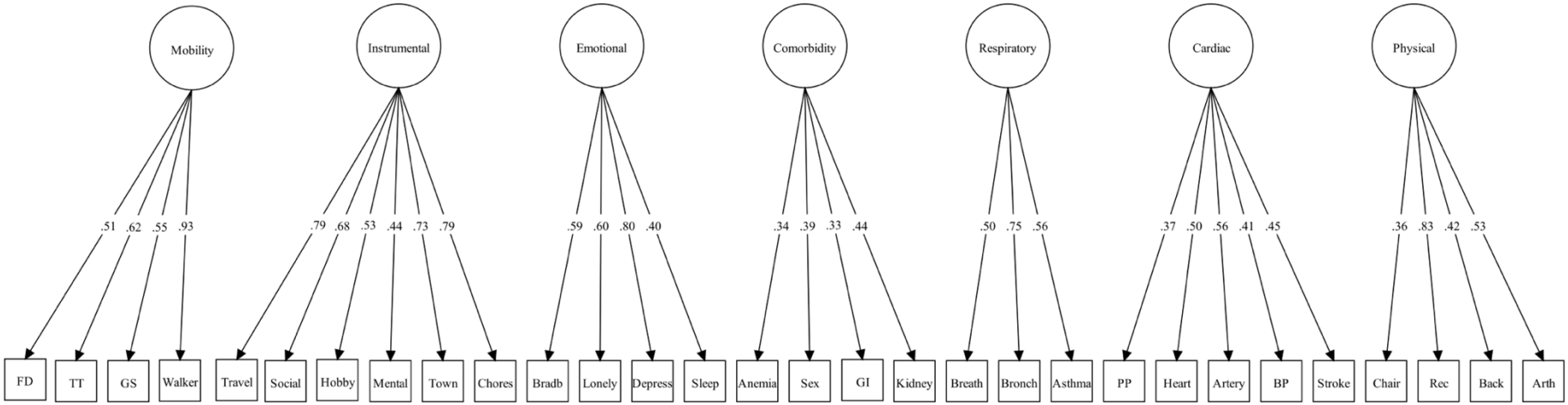


Figure S1. Confirmatory factor analysis model of multi-morbidity data. FD, finger dexterity; TT, timed turn; GS, grip strength; Walker, use of a walker, cane, or wheelchair; Travel, health has affected ability to travel; Social, health has affected ability to socialize; Hobby, health has affected ability to do hobbies; Mental, health has affected ability to do mental recreational activities; Town, health has affected ability to get around town; Chores, health has affected ability to do chores; Bradb, Bradburn negative affect; Lonely, during the past week I felt lonely; Depress, during the past week I felt depressed; Sleep, during the past week my sleep was restless; Sex, sex-related health problems; GI, gastrointestinal problems; Kidney, kidney or bladder trouble; Breath, feeling short of breath; Bronch, bronchitis or emphysema; PP, pulse pressure; Heart, heart trouble; Artery, hardening of arteries; BP, high blood pressure; Chair, stay at home but in chair most of the time; Rec, health has affected ability to do physical recreational activities; Back, spinal condition and/or back problems; Arth, arthritis. Standardized factor loadings are shown. All

loadings were significant at $p < .05$. Covariances and residuals are not depicted. Response scales for each item are outlined in Table 2-1.

Supplementary References

Dixon, R. A., Garrett, D. D., Lentz, T. L., MacDonald, S. W. S., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: Exploring the roles of speed and inconsistency. *Neuropsychology*, *21*(3), 381–399. doi: 10.1037/0894-4105.21.3.381

Dixon, R. A., Small, B. J., MacDonald, S. W. S., & McArdle, J. J. (2012). Yes, memory declines with aging-- but when, how, and why? In M. Naveh-Benjamin M & N. Ohta (Eds.). *Memory and aging: Current issues and future directions* (pp. 325-347). Psychology Press.

Little, T. D. (2013). *Longitudinal structural equation modeling*. Guilford Press.

McFall, G. P., Wiebe, S. A., Vergote, D., Anstey, K. J., & Dixon, R. A. (2015). Alzheimer's genetic risk intensifies neurocognitive slowing associated with diabetes in nondemented older adults. *Alzheimer's & Dementia: Diagnosis, Assessment, and Disease Monitoring*, *1*(4), 395–402. doi: 10.1016/j.dadm.2015.08.002

Singer, J. D., & Willett, J. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford University Press.